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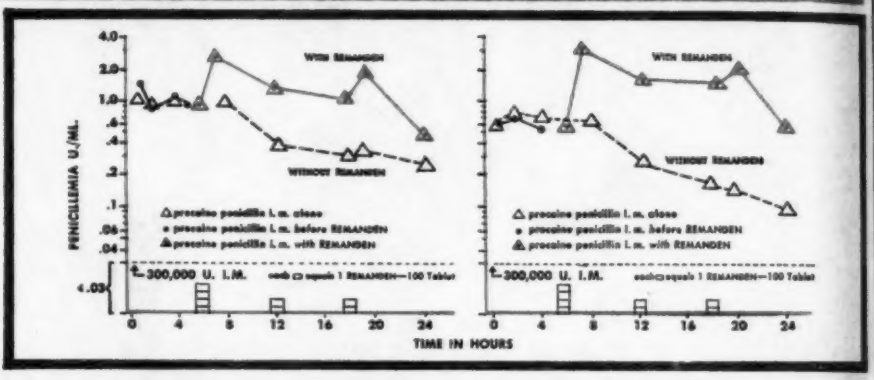

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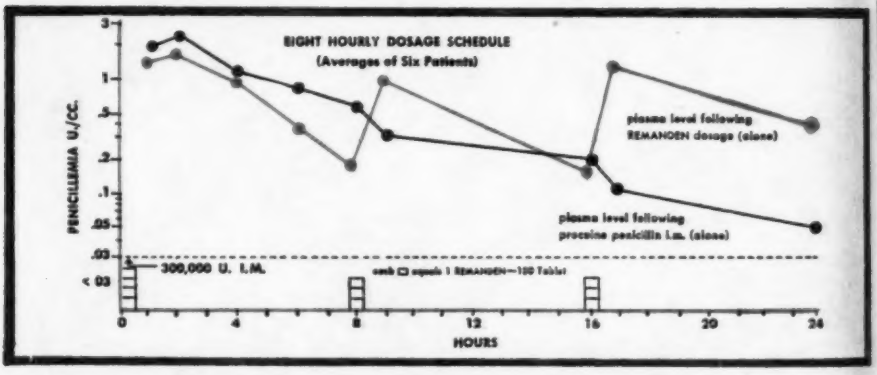
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RETENTION AND PERFORMANCE OF "SKILLED MOVEMENTS" AFTER CORTICAL ABLATIONS IN MONKEYS[1]

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INTRODUCTION

Campbell (4) first called attention to the structural characteristics of the so-called premotor cortex when he described the intermediate precentral area. He was impressed by its many similarities of cellular lamination and fiber structure to the precentral area. As to its possible functions he said: "I am of the opinion that this particular stretch of cortex is specially designed for the execution of complex movements of an associated kind, of skilled movements, of movements in which consciousness or volition takes an active part. . . ."

Brodmann (2) studied the field and designated it area 6. Later the Vogts (23) redefined its boundaries and subdivided it into several subareas. They considered it an area for the organization of complex, adversive and synergic movements. Finally Economo and Koskinas (7) designated it FB.

In 1932 Jacobsen (10, 11) reported on the effects of extirpating motor and premotor areas upon the retention and execution of acquired skilled movements in primates. He concluded that after unilateral lesions of the premotor area (defined according to the Vogts): "The organization of these movements as patterns of response to the specific situation presented by the problem boxes was greatly disturbed and necessitated postoperative relearning." Kennard, Viets and Fulton (13) reported "precocious disturbances of skilled movements" as the most significant feature of the "premotor syndrome" in man. Earlier in 1924 Lashley (16) had found retention of motor habits after lesions of the precentral motor area which also involved large parts of the intermediate precentral cortex.

[1] Aided by grants to C. N. Woolsey from the Research Committee of the University of Wisconsin out of funds supplied by the Wisconsin Alumni Research Foundation and by RG-B-35 from the Division of Research Grants and Fellowships, U.S.P.H.S.

[2] Instituto de Fisiologia, Escuela de Medicina, Universidad de Chile, Santiago, Chile.

[3] The author wishes to thank Prof. H. F. Harlow, Department of Psychology, University of Wisconsin, for the use of facilities in the Primate Laboratory, for the loan of testing equipment and for the use of the six normal monkeys which served as controls. She also wishes to thank Dr. Lashley for his kindness in lending the latch boxes for use at Wisconsin and especially to thank Dr. Woolsey for reading the manuscript and giving most helpful suggestions.

[4] Formerly Fellow in Physiology, The Johns Hopkins University School of Medicine.

Because of the apparent contradiction in the results of Jacobsen and of Lashley, it was decided, while the present author was working at Orange Park in 1949 under the direction of Dr. Lashley, to reinvestigate the problem of the premotor area as a locus for the retention of learned skilled movements. The results obtained then did not appear conclusive. Two animals having nearly complete premotor ablations appeared oriented and showed good retention with some of the problem boxes but with others they required a larger number of trials to reach a uniform performance than before operation. These same two animals (49-1, 49-2) also had some damage to the precentral motor area. One month after operation they failed to open some of the latches; two months after operation they succeeded. It was therefore uncertain whether the deficits noted were due to the premotor or to the precentral lesions. Likewise it was not clear whether final successful performance resulted from relearning or whether testing had been carried out prematurely before optimal recovery of motor capacity had taken place.

Recent electrical stimulation studies on motor areas of the frontal lobe of the monkey (26) have indicated the need for reexamining the evidence for the concept of a premotor cortex. In mapping the precentral motor area, it was demonstrated that the motor pattern hangs together much as does the actual musculature and that the accepted complete separation of face from trunk area by the intervening arm area is not correct. The part of the pattern which binds together face, arm and leg subdivisions is that for the axial musculature. This forms the rostral portion of the precentral motor area and its anterior border corresponds approximately to the boundary between the Vogts' (23) areas 6 aα and 6 aβ. Only pupillary dilatation was produced by threshold stimulation of dorsal area 6 rostral to this boundary. From the total pattern defined it seems clear that Bucy's (3) area 6 motor responses and the synergic movements obtained by the Vogts on stimulating area 6 on the dorsal aspect of the hemisphere must have been due to stimulation of the rostral portion of Woolsey's precentral motor field which activates the axial musculature (26).

There exists, however, on the medial wall of the hemisphere, in a part of area 6, another motor field which Penfield and Welch (17) have designated in man the "supplementary" motor area. Since the 1880's (8) it has been known that stimulation of this part of the cortex may give movements of the arm and the neck. The Vogts considered this area a continuation of the adversive, synergic field of dorsal area 6. However, it has now been demonstrated (26) that in the supplementary motor area of the monkey there is a complete representation of the contralateral body musculature. The pattern is so disposed that the lower face is represented nearest the dorsal edge of the hemisphere at the level of the rostral end of the corpus callosum. The upper face, ear, neck, back and tail are represented in rostrocaudal sequence along the deepest part of the upper bank of the sulcus cinguli. Fingers are represented at the edge of

the hemisphere just ahead of the precentral motor area, while more proximal parts of the arm are activated from points between the finger area and the deeper parts of the sulcus cinguli. The hind limb representation is entirely within the sulcus cinguli with the apex of the limb reaching back to the level of the central sulcus.

As a consequence of these studies several questions arose. Was the impairment of skilled movements reported for "premotor lesions" the result of damage to the rostral portion of the precentral motor area? Could the effects be attributed to the supplementary motor area, or to removal of dorsal area 6, whose stimulation produced no somatic movements? What roles did relearning and recovery of motor capacity with the passage of time play in the ability of animals to carry out skilled movements after various cortical ablations? To obtain the required answers it seemed essential that the lesions be bilateral.

That areas 4 and 6 might be removed bilaterally in adult monkeys with preservation of locomotion was indicated by an earlier report of Woolsey and Bard (25) who made serial ablations over a considerable period of time in one animal. Recently Travis and Woolsey (20) prepared gradually several animals with bilateral removal of precentral and supplementary motor areas, leaving only the precentral face areas. These animals continued capable of walking and feeding themselves. These results encouraged us to train some of these animals in motor tests. We were able, in fact, to test one animal after nearly complete bilateral removal of the whole frontal lobe.

MATERIALS AND METHODS

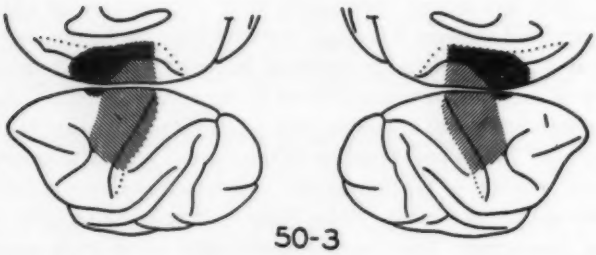
Animals. Seventeen animals, previously untrained, were used in this study. Four of these were prepared and studied at Orange Park (49-1 to 49-4). The brains were removed after perfusion and fixation in 10 per cent formalin. They were sectioned in the Phipps Neurological Laboratory and the gross lesions were reconstructed by the author in the Department of Physiology, The Johns Hopkins University, School of Medicine. The results are charted in Figure. 3.

Seven were prepared and studied at the University of Wisconsin (50-3, 50-10, 50-70, 50-74, 50-79, 50-149, 50-150). The lesions are illustrated in Figures 1 and 2, except for those of 50-74, which are shown in Travis (18), Plate XIX, Figure 6. The brains of animals 50-70, 50-79, 50-149 and 50-150 were perfused and fixed in 10 per cent formalin and then sectioned at the Phipps Neurological Laboratory, The Johns Hopkins University, School of Medicine. Dr. Konrad Akert kindly studied the lesions and provided the illustrations. More detailed descriptions of the lesions together with reports on thalamic degenerations will appear elsewhere (1).

Animals 50-3, 50-10 and 50-74 were used in another study in which additional lesions were made. The placement of the lesions pertinent to this study were controlled at operations by electrical stimulation and by knowledge of the pattern of localization acquired in the study of the precentral and supplementary motor areas referred to above. The lesions as defined by the operative notes are illustrated in Figure 1.

All ablations were made with animals under pentobarbital anesthesia by Dr. Clinton Woolsey, who employed the subpial aspiration technic and worked with a Beebe binocular

50-70



50-3

50-10

FIG. 1. Dorsal, lateral and medial views of the brain of monkey 50-70 showing the lesions as reconstructed from serial sections. The black indicates complete removal of cortical tissue; the dotted areas signify that only the superficial layers were removed. An old accidental injury to the left occipital lobe was found.

Monkey 50-3 was studied (1) after the precentral arm, leg and trunk areas (lined) had been removed bilaterally in four successive operations at 3 month intervals, and (2) after bilateral removal of supplementary motor areas (cross-hatched). The illustrations were constructed on the basis of operative notes and the appearance of the brain, when exposed for subsequent further cortical removals.

Monkey 50-10 was studied after each of four successive operations: (1) Bilateral precentral removal (lined), (2) bilateral dorsal area 6 removal plus removal of right orbitofrontal and anterior cingulate regions (cross-hatched), removals of bilateral supplementary motor areas (black), and (4), removal of left orbitofrontal and anterior cingulate areas (dots).

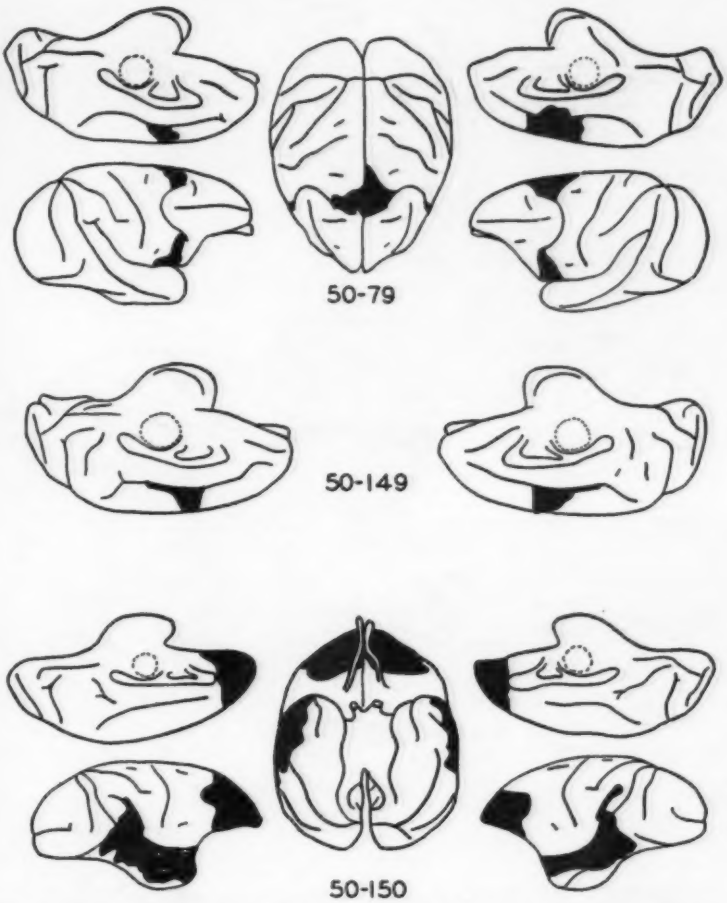


FIG. 2. Charts of brain lesions in monkeys 50-79; 50-149 and 50-150, as reconstructed from serial sections.

loupe. The dura was always closed with fine continuous silk surtures and the bone flaps were replaced. The Wisconsin animals were all studied neurologically by A. M. Travis and for the purposes of her study the lesions were made in stages. These neurological studies have been reported separately (18, 19, 20, 21 and 22). Some of these animals were tested by me only after the final operation; others were studied at various stages. Photographs of the final state of the brains of several of the animals appear in the Travis papers.

Six animals served as controls. They were naive animals of the Primate Laboratory, University of Wisconsin (Numbers 156, 157, 158, 159, 162, 164).

Testing apparatus. The problem boxes used were those illustrated in Jacobsen's (9) Figures 1 to 8. These had to be opened to obtain concealed food rewards. In addition to the preliminary *rope box* there were two series. Series A included the *pull box*, the *crank box*, the *hook and handle box* and *combination box A*, a composite of the preceding three. Series

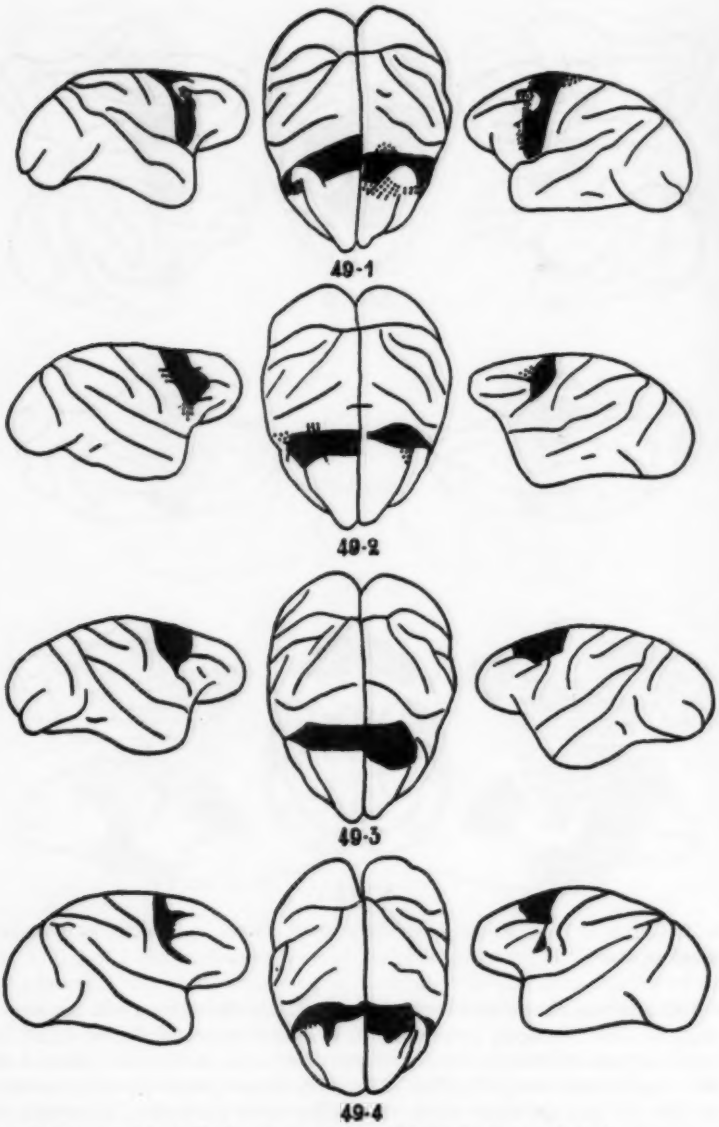


FIG. 3. Charts of brain lesions in monkeys 49-1, 49-2, 49-3 and 49-4 as reconstructed from serial sections. The dotted areas indicate superficial damage to the cortex.

B consisted of a *slide box*, a *ring box*, a *hasp box*, and *combination box B*, which was compounded of the other three. The crank box differed from that illustrated by Jacobsen in that the crank was at the right hand end. The crank had to be turned clockwise approximately 300 degrees. It was set at "8 o'clock" and had to be turned to "6 o'clock".

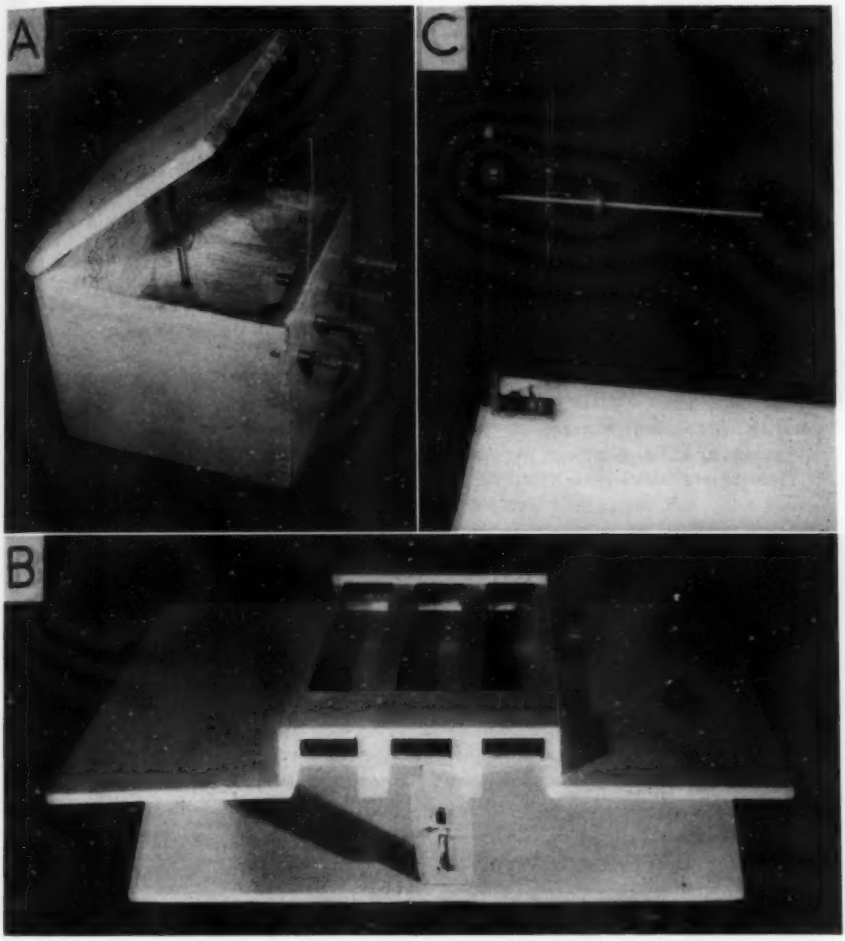


FIG. 4. Push-pull box. The animal must operate the four rods that project from the front of the box. The first three rods, going from left to right must be pushed before the fourth rod, which releases the lid, can be pulled. B. Peanut slide. The peanut can be sent down in either of the three channels shown in the photograph. The monkey must catch the peanut on its way down before it disappears into the box beneath the lower cover. C. Life-saver bar. The animal must remove the life-saver placed on the rod.

To these two sets was added another box called the *push-pull* box (Fig. 4A). This was similar in principle to one described by Jacobsen, Wolfe and Jackson (12). It was made of wood and measured 8 x 8½ x 9 inches. Four metal rods, 2 inches long, set 1½ inches apart, projected from the front of the box. The rods were numbered 1 to 4 from left to right in the order in which they were to be operated. Rods 1 to 3 had to be pushed, rod 4 pulled. A concealed mechanism was so arranged that rod 1 had to be pushed and left in before rod 2

could be pushed; likewise 2 had to be in before 3 could be pushed and rods 1, 2 and 3 had to be in before 4 could be pulled to open the box.

Two new tests were added. In these the food was in sight of the animal. They were named the *peanut slide* and the *life-saver bar*. The peanut slide (Fig. 4B) was an inclined plane made of a piece of plywood 24 inches square, in the center of which were three channels 2 inches wide. The upper and lower ends of the channels were covered. The peanut was placed, under cover, in one of the channels and sent down the slide. The animal had to catch the peanut before it disappeared into a box beneath the lower cover. The inclination of the slide could be varied so the peanuts could be made to descend at different rates. Four different angles of inclination were used: 12.5, 25, 35 and 45 degrees. The life-saver bar (Fig. 4C) was a ⅛ inch metal rod 7½ inches long. It was attached to a metal post mounted on a board. The free end of the bar could be set to point either to the right or to the left. A candy life-saver placed on the rod near the post had to be removed by the animal.

A special room was used for testing. The animal was brought from its living-cage to the testing room where it was placed in a cage with vertical bars through which it could reach. The problem boxes and the life-saver bar were baited in view of the animal and moved toward it across a table on a carrying tray to which each piece of apparatus could be attached. The peanut slide was placed on the table directly before the cage grill.

Training procedures. Before formal testing started the animals were brought to the testing room daily for at least 10 days. They were fed by the experimenter and a special effort was made to get them used to the carrying tray.

The animals studied at Orange Park were trained only on the latch boxes. Animals 49-2 and 49-4 were tested only with Series A problem boxes; animals 49-1 and 49-3 were tested only with Series B. It was our impression then that Series A, particularly the crank box, was more useful for revealing deficits in these animals. For this reason the Wisconsin animals were trained on Series A alone, except for monkey 50-10 who was tested on the crank box and on the slide and the hasp boxes and on combination box B.

At Wisconsin the tests were given each monkey in the following order: 1) The peanut slide; 2) the rope box; 3) the pull box; 4) the crank box; 5) the hook and handle box; 6) combination box A; 7) the push-pull box; 8) the life-saver bar.

Animals were trained on the peanut slide by allowing them to practice catching raisins, grapes and other pieces of food rolled down the slide. As training progressed changes in the inclination of the slide were made more frequently. When the animals were accustomed to the apparatus and consistently made efforts to get the reward, formal testing was begun. A series of 200 critical trials was given to the normal controls and to the experimental group. The maximal number of trials a day was 40. The channel in which the peanut was dropped and the angle of the board were changed at random. Salted Spanish peanuts were used and an effort was made to choose the roundest. The number of peanuts missed at each session was recorded. At least 20 seconds elapsed between trials. The control group received a second series of 200 trials after 6 months. It was not considered necessary to give them a third series because their performance appeared to plateau. The operated animals had their second series after they were considered adequately recovered.

Training on the problem boxes was initiated with the rope box. Training was discontinued when the animals were able to open each box consistently with little or no random movement in approximately the same length of time. On the crank box the animals got some help in the first three trials. The crank, instead of being set at "8 o'clock", was set at "3 o'clock". The elements of the hook and handle box were dissociated in the first 3 to 6 trials. The combination box was presented as such at the first trial.

With the push-pull box an attempt was made to present the whole problem from the

start, but no monkey was able to open it after one hour's presentation on three successive days, nor when the box was left with the animal overnight for three nights. The box was then presented with rod 4 alone set. When this was mastered, rod 3 was set, then rod 2 and, finally, rod 1. Only the experimental animals were trained on this box.

A record was kept of the number of trials that each animal needed to learn each problem and of the time required for each trial. Notes were kept of the pattern of movements employed and of the use of right and left hands. Usually training was continued for about 30 minutes each day. Retention was studied on the control group after 6 months. A third series was considered unnecessary, since performance plateaued in the second series.

With the life-saver bar a procedure very similar to that used with the latch-boxes was followed. Five pretesting trials were given with the bar pointed toward the monkey. Then the bar was presented pointing to right or to left at random. No more than 6 trials a day were given in this test. All the animals used for ablations liked the candy, but two in the control group were not motivated by this lure. Besides the candy a piece of some preferred food was added at the end of every trial. Training was discontinued when uniform performance was reached. The control group was tested again after 6 months.

RESULTS

A. Precentral Motor Area

1. Bilateral ablation of precentral arm area. Two animals (50-70, 50-74) were trained before and after complete bilateral ablation of the precentral arm area. Testing of both animals was begun 4 months after operation.

a. Results on the peanut slide test. Curve 4, Figure 5 shows the mean percentage error for both monkeys, after the operation indicated by the first arrow. Each unit on the abscissa represents 40 trials (approximately the number of trials per day). After removal of the arm areas there was a significant increase in the number of peanuts missed ($t = 16.2$; df $= 38$; p. $< .001$). The animals were unable to catch a single peanut when the slide was at its two highest positions (35 and 45 degrees). When the slide was at 25 degrees monkey 50-70 missed 77 per cent of the peanuts as compared with 23 per cent before operation. Monkey 50-74 missed all at this position of the slide. There was no improvement of performance in this test throughout the postoperative training period.

b. Results on the problem boxes. It was clear as soon as the boxes were presented that the animals were well oriented. They started to work immediately. Since the *pull box* never revealed any difference between the normal controls and any operated animal, except 50-150, results for it will not be presented.

The results on the *crank box* test are given in Table I. The records of the controls and the experimental group during the learning and the retention trials are shown. Postoperatively the monkeys with precentral arm lesions showed good retention of the habit. The minimal time per trial (M) was not as good as the corresponding preoperative value. The record of monkey 50-70 was inferior to that of 50-74, in spite of the fact that the former seemed to have in general better manual dexterity. However, this is accounted for by the relative deficits of the right and left arms in the two monkeys and the position of the crank.

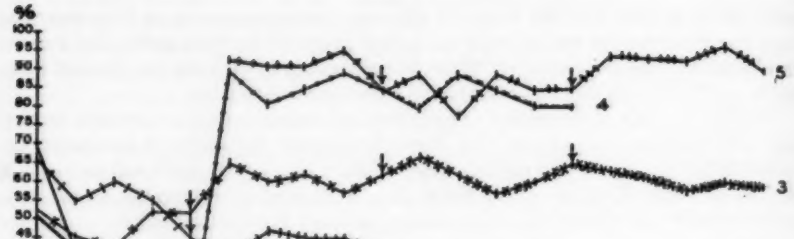


FIG. 5. Results on the peanut slide. Percentage of failures on ordinate. On the abscissa each unit represents 40 trials. The arrows on each curve indicate from left to right the successive operations.

Curve 1: Normals. First test series and second series after 6 months. *Curve 2:* Monkey 50-149. Normal series, and series after bilateral supplementary motor ablations. *Curve 3:* Monkey 50-79. Normal series and series after (a) bilateral supplementary plus partial precentral ablations, (b) after addition of bilateral dorsal area 6 lesion, and, (c) after addition of lateral area 6 lesions. *Curve 4:* Mean percentage for monkeys 50-70 and 50-74. Normal series and series after (a) bilateral precentral arm lesions and (b) after added removal of both precentral leg areas. *Curve 5:* Mean percentage for monkeys 50-3 and 50-10. No normal series. (a) Series after bilateral ablation of precentral arm and leg areas, combined scores for both monkeys; (b) results from 50-10 alone after additional bilateral removal of dorsal area 6 plus right orbitofrontal and anterior cingulate cortex; (c) combined scores for 50-3 and 50-10 with the lesions illustrated in Figure 1.

Monkey 50-74 had better use of his right hand and so was better able to manipulate the crank than was 50-70.

Table II shows the results on the *hook and handle box test.* Both animals showed good retention. Monkey 50-74 did not achieve his minimal preoperative time, apparently because of the marked impairment of his left hand. He had to readjust and change his pattern of movement. Before operation both animals opened this box with the left hand alone. They were able to lift the handle and to shift to the hook before the handle completed its fall. After operation, 50-70 was unable to do this. He had to learn to lift the handle with his right hand and then using the left hand as a claw, to draw out the hook and transfer it to the right hand and so lift the lid to which the hook was attached. Transfer of the hook thus lengthened the procedure. Monkey 50-70, still relatively more skillful with his left hand, did not modify his pattern of movement.

The results on *combination box A test* are shown in Table III. The operated

TABLE I

Results for the Crank Box Test

Average time in seconds consumed in opening the box by the control normals and experimental group

Learning trials—Control group							Learning trials—Experimental group								
Subjects / Trials	159 N	156 N	157 N	154 N	162 N	158 N	49-2 N	49-4 N	50-70 N	50-74 N	50-79 N	50-149 N	50-150 N	50-10 PC.A.L.	50-3 PC.A.L.
1–3	15	8	2	15	23	14	75	5068	49	157	40	5	197	66	186
4–6	13	4	16	2	27	2	6	290	20	9	48	1	268	37	140
7–9	3	1	1	*M1*	5	*M1*	3	238	101	14	29	*M1*	223	29	32
10–12	*M2*	*M1*	*M1*		*M2*		*M2*	1155	2	15	41		35	7	103
13–15								197	*M1*	8	*12*		35	*M6*	115
16–18								75		3	*M4*		92		99
19–21								128		*M2*			24		56
22–24								7					12		10
25–27								3					5		9
28–30								*M2*					2		13
31–33													*M1*		10
34–36															11
															M9

Retention trials—Control group							Post-operative retention trials. Experimental group								
After 6 months							Area 6 P.PC		6D	PC. A.	PC. A.	Supp.	Supp.	T.	PC.A.L. 6D	PC.A.L. Supp.
1–3	10	3	1	4	2	2	4049	31	25	27	5	344	56	3	78	
4–6	2	2	2	2	1	1	267	22	3	39	5	65	30	2	23	
7–9	*M2*	*M1*	*M1*	*M1*	*M1*	*M1*	29	30	*M2*	10	*M4*	13	*M1*	*M1*	6	Failed
10–12							28	12		7		8			*M4*	
13–15							43	12		6		7				
16–18							40	22		*M4*		3				
19–21							33	5				*M3*				
							M24	*M4*								
										PC. A.L.	PC. A.L.	Supp. 6D		T. O.F.	PC, 6D Supp.	
1–3										6	3	2		38		
4–6										5	2	2		49		
7–9										*M5*	*M2*	*M1*		*M16*	Failed	
												Supp. 6D, 6L		After 2 Mo.		
1–3												2		6		
4–6												1		2		
												M1		*M1*		

Average time in seconds consumed in opening the crank box by the normal and experimental animals. Each column is headed by an animal's number. The results obtained during the first period of training for normal controls and experimental animals is shown in the upper half of the Table. Results for successive periods of training are found in the lower half of the Table. For normal controls the scores in the lower half correspond to the retention trials after six months; for experimental animals the scores correspond to the second, third or fourth period of training after each successive operation. Animals 50-3 and 50-10 differed from the others in that their first training period came after several operations. A = arm. 6D = dorsal portion of cortical area 6. 6L = lateral portion cortical area 6. L = leg. M = best performance achieved. N = normal. O.F. = orbito-frontal region of cortex. P = partial. PC = precentral cortical region. Pre-op = preoperative. Supp = supplementary motor area of the cortex. T = temporal neocortex. ⌐→ = Results of trials two months after the operation.

TABLE II

Results for the hook and handle box test

Average time in seconds consumed in opening the box by the control normals and experimental group

	Learning trials—Control group						Learning trials—Experimental group						
Subjects / Trials	159 N	156 N	157 N		164 N	162 N	158 N	49-2 N	49-4 N	50-70 N	50-74 N	50-79 N	50-149 N	50-150 N
1–3	62	11	57	4	7	54	15	240	1228	93	163	31	29	91
4–6	240	312	5	2	35	7	218	35	110	16	20	9	449	9
7–9	371	164	15	M2	16	50	115	11	61	12	49	57	21	14
10–12	78	73	31		109	45	27	10	9	10	4	59	7	16
13–15	33	68	15		15	439	83	196	7	32	23	8	21	66
16–18	37	34	33		58	220	40	64	6	8	214	14	23	29
19–21	29	17	122		58	55	8	236	7	16	130	11	6	16
22–24	14	11	10		13	57	14	112	20	9	13	16	64	11
25–27	16	7	17		10	18	14	12	6	3	13	11	12	15
28–30	8	29	12		16	17	225	45	2	*M2*	26	12	13	2
31–33	10	6	11		19	14	30	115	*M2*		20	8	3	*M2*
34–36	7	7	8		7	7	8	13			12	2	*M3*	
37–39	9	16	7		5	10	6	12			5	*M2*		
40–42	9	16	7		*M7*	*M5*	6	15			3			
43–45	*M3*	*M2*	5				*M2*	*M8*			*M2*			

	Retention tests—Control group						Post-operative retention trials—Experimental group					
	After 6 months						Area 6, P.Pc	6D	PC.A	PC.A	Supp.	Supp.	T.
1–3	7	3	7	2	6	1	129	16	128	7	26	4	3	5
4–6	2	2	3	2	4	2	92	32	31	6	6	2	1	5
7–9	M2	M2	M1	M2	M2	M1	74	11	8	*M3*	*M5*	*M2*	*M1*	2
10–12							98	3	33					*M2*
13–15							85	*M5*	*M2*					
										PC. A.L.	PC. A.L.	Supp. 6D		T.O.F.
1–3										20	26	2		+2 hours
4–6										8	6	1		+3 hours
7–9										*M4*	*M6*	*M1*		+3 hours
												Supp. 6D, 6L		After 2 Mo.
1–3												2		6
												M1		*M2*

= Results of trials 17 to 31 and 46 to 51 of monkeys 49-2 and 157 respectively. For the general arrangement of this Table see legend on Table I.

animals, having already adjusted to their new condition on the preceding boxes, did not show any clear differences from the control group in the number of trials and time per trial.

Data for the *push-pull box test* are given in Table IV. It is clear from the num-

TABLE III

Results for the combination box A

Average time in seconds consumed in opening the box by the control normals and experimental group

Learning trials—Control group							Learning trials—Experimental group							
Subjects / Trials	159 N	156 N	157 N	164 N	162 N	158 N	49-2 N	49-4 N		50-70 N	50-74 N	50-79 N	50-149 N		50-150 N
1–3	38	78	62	128	23	46	33	263	12	403	154	186	195	10	52
4–6	44	33	36	58	8	24	32	221	13	131	118	10	40	25	49
7–9	51	75	13	75	15	8	17	123	8	128	161	14	47	16	107
10–12	33	107	60	40	50	30	65	54	10	118	242	34	117	17	17
13–15	77	47	86	21	10	8	21	51	7	19	202	19	140	15	15
16–18	49	49	34	6	15	6	20	26	*M7*	22	42	11	85	22	11
19–21	38	14	58	*M6*	8	*M5*	22	168		27	216	5	53	9	31
22–24	19	62	12		*M6*		19	123		13	36	*M5*	58	33	8
25–27	13	6	11				20	52		7	154		44	*M6*	*M6*
28–30	8	*M4*	23				25	40		*M5*	67		38		
31–33	*M7*		21				19	14			12		70		
34–36			18				9	30			20		31		
37–39			13				*M7*	29			6		30		
			M7								*M6*		61		

Retention tests—Control group							Post-operative retention trials—Experimental group						
	After 6 months						Area 6 P.PC.	6D	PC.A.	PC.A.	Supp.	Supp.	T.
1–3	9	7	12	6	8	7	52	55	12	90	14	29	36
4–6	8	6	8	9	10	7	98	24	7	30	13	5	13
7–9	*M6*	*M5*	*M5*	*M6*	*M7*	*M5*	51	16	7	25	*M12*	*M4*	8
10–12							*M10*	*M7*	*M7*	26			*M4*
13–15										10			
										M8			
									PC.A.L.	PC.A.L.	Supp. 6D		T.O.F.
1–3									15	90	15		
4–6									11	30	10		
7–9									7	25	*M9*		Failed
10–12									*M7*	*M10*			
											Supp. 6D, aL		After 2 Mo.
1–3											17		Not
4–6											11		tested
											M8		

⌐¬ = Results of trials 46 to 60 and 31 to 54 of monkeys 49–4 and 50–149, respectively. For general arrangement of this Table see legend on Table I.

TABLE IV

Results for the push-pull box test

Average time in seconds consumed in opening the box by the experimental group

Learning trials. Experimental group											Post-operative retention trials. Experimental group					
Subjects	50-70 N		50-74 N		50-79 N		50-149 N		50-150 N		Subjects Trials	50-70 PC.A.	50-74 PC.A.	50-79 Supp.	50-149 Supp.	50-150 T.
Trials	No. rods set		No. rods set		No. rods se		No. rods set		No. rods set							
1–3	1	12	1	12	1	13	1	89	1	60	1–3	29		44	21	75
4–6	1	5	1	15	1	7	1	3	2	303	4–6	12		165	32	3
7–9	2	46	1	2	2	55	2	111	2	16	7–9	*M6*		94	33	9
10–12	2	10	2	5	2	6	2	11	2	1	10–12		Failed	247	19	*M2*
13–15	2	10	2	215	3	239	2	63	3	34	13–15			63	*M5*	
16–18	2	3	2	162	3	65	2	67	3	118	16–18			20		
19–21	3	41	2	33	3	34	2	47	4	88	19–21			41		
22–24	3	8	2	9	3	29	2	1	4	41	22–24			17		
25–27	3	7	2	105	3	8	3	63	4	71	25–27			8		
28–30	4	82	2	27	3	57	3	1	4	52				*M7*		
31–33	4	35	2	50	3	9	4	32	4	58						
34–36	4	50	2	46	4	58	4	76	4	40		PC. A.L.	PC.A.L.	Supp. 6D		T.O.F.
37–39	4	13	2	8	4	47	4	126	4	26						
40–42	4	5	2	26	4	35	4	236	4	25	1–3	70		39		
43–45	4	12	2	16	4	49	4	27	4	47	4–6	47		15		
46–48	4	21	2	2	4	28	4	28	4	8	7–9	63	Failed	21		Failed
49–51	4	8	2	2	4	33	4	32	4	5	10–12	13		8		
52–54	4	15	3	31	4	58	4	36	4	44	13–15	9		*M6*		
55–57	4	28	3	16	4	24	4	32	4	16		*M8*				
58–60	4	6	3	12	4	7	4	50	4	5						
61–63	4	7	3	6	4	11	4	69	4	51				Supp. 6D, 6L		After 2 Mo.
64–66	*M3*		3	7	4	38	4	23	4	11						
67–69			4	10	4	8	4	24	4	4						
70–72			4	87	*M5*		*M9*		*M3*		1–3			51		14
73–75			4	108							4–6			18		*M8*
76–78			4	72							7–9			9		
79–81			4	43										*M6*		
82–84			4	10												
85–87			4	32												
89–90			4	8												
			M4													

Average time in seconds consumed in opening the push-pull box by the animals of the experimental group. On the left side of the Table the scores correspond to the first period of training. On the right side are presented the scores for the second, third or fourth periods of training after each successive operation.

ber of trials required that all monkeys tested on this box had difficulty learning it. (The controls were not trained on it.) All animals used both hands to work this box. The following behavior at the end of the training period was typical. First an attempt was made to pull out rod 4 with the right hand. Then attention

was switched to rods 1 and 2 and each rod was alternately pushed and pulled with the corresponding hands. This activity was interrupted intermittently to check on rods 3 and 4 in the same way. Rod 1 was then pushed in and left and attention was next given to rods 2 and 3. Then, leaving 2 in, rods 3 and 4 were manipulated and the box opened. At the end of training, this period of trial and error usually lasted for 3 to 16 seconds, but once rods 1 and 2 were accidently left in the correct position, rods 3 and 4 were handled efficiently. Monkey 50-70 was able to work this box after operation with the same pattern of movement. Monkey 50-74 was unsuccessful in four sessions on consecutive days. In the first session he attempted to pull out rod 4, but he was unable to go further. His failure seemed related to the difficulty of using his left hand except as a claw. Prolonged observations of normal animals led to the impression that to solve the problem this operated monkey would have to acquire not only a new motor pattern but an insight which no other monkey seemed to exhibit.

c. Results on the life-saver bar test. Taking a life-saver candy off a bar was not an easy task for a monkey. During the process of learning he usually used one hand to move the candy in one direction and the other to move it in the opposite direction. After training, the animal used only the right hand when the bar was pointing to his right and the left hand when the bar pointed to his left. At the end of the first training period the time required to remove the candy was rather long (Table VIII). But in the first or second trial of the second training period the task could be performed in one to two seconds. All the normal animals and some of the operated ones were able to achieve this speed in the second training period and occasionally in the first. Monkey 50-70 needed as many trials post-operatively as before to reach uniform performance. However, he was able finally to surpass the preoperative records of both hands. The performance of monkey 50-74 was quite uniform after surgery but his movements were slower than for any monkey of the control group. His shortest time was not greater than before operation, but it was definitely slow for a second period of training. In spite of the greater motor impairment of the left hand in this animal, his minimal time per trial was equal to that for the right, because he learned to push the candy off the bar instead of sliding it off by grasping it.

2. Bilateral ablation of precentral arm and leg areas. Monkeys 50-70 and 50-74 were subjected to second operations in which the precentral leg area was removed bilaterally. The total lesions after these operations are shown for 50-70 in Figure 1 and for 50-74 in Plate XIX, Figure 6 of Travis (18). The animals were retested 10 weeks later. Two other monkeys (50-3 and 50-10) were tested for the first time after bilateral removal of the precentral arm and leg motor areas in four stages (Fig. 1). Training of 50-3 was begun 4 months after removal of the second arm area and 10 months after removal of the second leg area. Monkey 50-10 began training 6 months after removal of the second arm area and 6 weeks after ablation of the second leg area. The performance of these two

animals will be compared with the learning trials of other monkeys, although comparison of the data is difficult because of the great variability of performances of monkeys during the learning period. This disappears when the problem has been learned, as can be seen in the retention tests of the controls made 6 months after initial training. For this reason no conclusion about speed of learning in these animals will be drawn. We shall comment only on obvious differences in the execution of the tasks.

a. Results on the peanut slide test. There was no significant change in the performance of 50-70 and 50-74 after bilateral removal of the precentral leg areas as compared with their performance after removal of the arm areas alone ($t = 1.75$; df = 18; p. = 0.1). These results are shown in curve 4, Figure 5, after the second arrow. For a period of 10 days monkeys 50-3 and 50-10 received the same preliminary training on the peanut slide as had been given the other monkeys in their initial training. They also had six days additional practice to give them an amount of training equal to that received by 50-70 and 50-74. The average percentage failure for monkeys 50-3 and 50-10 is shown in curve 5, Figure 5. No significant difference between the two groups was found. All the animals showed severe impairment of ability to catch peanuts even with the slide set at 12.5 degrees, and they failed completely when the angle was increased to 25 degrees.

b. Results on the problem boxes. Monkey 50-70 was very uniform in his performance with the latch boxes, but was consistently slower than after removal of arm areas alone. Monkey 50-74 did as well as before and even improved his performance (Tables I, II, III, IV). Monkey 50-10 appeared to learn these problems as readily as normal monkeys. The types of movements employed were similar to those used by the other precentral animals. In the results with the slide box and combination box B, he was comparable in number of trials and minimal time to the normals tested at Orange Park. Monkey 50-3 was tested on the pull and crank boxes. She did as well on the first as did normal monkeys. However, she was unable to operate the crank box in the manner of other monkeys. It was necessary to teach her gradually to move the crank. First, the crank was set at "3 o'clock", then at "1, 11 and 8 o'clock", until she mastered each stage. But she never was able to turn the crank in one movement. Her final pattern was as follows: She would lift the crank to approximately "11 o'clock" with her right hand and then with great effort using both hands, she would lift it to "12 o'clock". At this point the right hand, assisted largely by gravity, moved the crank down. Her best time was 9 seconds, the slowest performance in this test of any animal with removal of the precentral motor cortex.

c. Results on the life-saver bar test. Monkey 50-70 achieved the peak performance reached after the arm area lesions (Table VIII). However, the number of trials required by the right hand to achieve this optimum was greater than for the controls (Table VII). This is especially significant since it was his third

TABLE V

Results for the slide box test

Subjects / Trials	49-1 N	49-3 N	50-10 PC.A.L. 6D
	Learning trials		
1–3	490	536	30
4–6	13	211	10
7–9	7	100	17
10–12	20	8	*M2*
13–15	5	3	
16–18	3	*M2*	
	M2		
	Post-operative retention trials		
	Area 6 P. PC.	6D	PC.6D Supp.
1–3	218	17	5
4–6	127	3	10
7–9	68	*M2*	4
10–12	52		*M2*
13–15	21		
16–18	27		
19–21	23		
22–24	13		
25–27	8		
	M2		
			PC.6D Supp. O.F.
1–3			6
4–6			7
7–9			4
			M2

Average time in seconds consumed in opening the slide box by three animals of the experimental group.

period of training. The performance of 50-74 remained uniform, but again, as was the case after the arm area removal, his best was poorer than the performance of normals. Monkey 50-10 did as well in this test as 50-74. He was able to remove the life-saver in 7 seconds with his right hand and in 9 seconds with the left. Monkey 50-3 reached uniform performance in approximately the same number of trials as the controls but her minimal time was longer than that of the other precentral monkeys.

B. "Premotor" Ablations

Under this category we shall describe the effects of various ablations which involved the so-called premotor area, or area 6 as variously defined.

TABLE VI

Results for the combination box test

Subjects / Trials	49-1 N	49-3 N	50-10 PC.A.L. 6D
		Learning trials	
1–3	3029	641	1460
4–6	2044	569	186
7–9	180	654	24
10–12	90	564	92
13–15	52	655	15
16–18	61	125	12
19–21	23	13	6
22–24	18	205	*M4*
25–27	8	18	
28–30	8	36	
31–33	*M5*	55	
34–36		49	
37–39		55	
40–42		49	
43–45		12	
46–48		6	
		M6	
		Post-operative retention trials	
	Area 6 P. PC.	6D	PC.6D Supp.
1–3		9	234
4–6		84	32
7–9	Failed	25	29
10–12		15	15
13–15		*M9*	8
			M6
	After 2 Mo.		PC.6D Supp. O.F.
1–3	77		93
4–6	62		24
7–9	41		16
10–12	38		*M7*
13–15	35		
16–18	29		
19–21	25		
22–24	20		
25–27	14		
28–30	11		
31–33	7		
	M6		

Average time in seconds consumed in opening the combination box B by three animals of the experimental group.

TABLE VII

Results on the life-saver bar test A

156 N		157 N		158 N		162 N		50-70 N		50-74 N		50-79 N		50-149 N		50-150 N		50-10 PC.A.L.		50-3 PC.A.L.	
R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
19	12	6	14	10	13	9	11	15	16	20	15	14	17	10	15	18	24	10	6	9	14
After six months.								PC.A.		PC.A.		Supp.		Supp.		T.		PC.A.L. Supp.		PC.A.L. Supp.	
6	3	6	6	6	6	4	7	16	12	6	6	6	6	6	9	4	9	12	6	14	16
								PC.A.L.		PC.A.L.		Supp. 6D*									
								15	7	6	6	5	4								

* With Supp., 6D, 6L: R = 3, L = 3.

Total number of trials required by monkeys with their right and left hand to reach best performance. R-right, L-left. For the general arrangement of this table see legend in Table I.

TABLE VIII

Results on the life-saver bar test B

156 N		157 N		158 N		162 N		50-70 N		50-74 N		50-79 N		50-149 N		50-150 M		50-10 PC.A.L.		50-3 PC.A.L.	
R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
8	2	2	2	2	1	3	2	9	6	7	7	5	7	1	2	1.5	2	7	9	11	13
After six months								PC.A.		PC.A.		Supp.		Supp.		T		PC.A.L. Supp.		PC.A.L. Supp.	
1	2	2	2	1	1	1	1	3	3	4	7	5	3	0.6	2	2	2	9	19	13	15
								PC.A.L.		PC.A.L.		Supp. 6D*									
								3	2	8	7	3	1								

* With Supp., 6D, 6L: R = 2, L = 1.

Maximum speed in seconds achieved by the monkeys with the right and left hand in the life saver bar test. For the general arrangement of this table see legend in Table I.

1. Bilateral ablation of the supplementary motor area. This area occupies a portion of area 6 on the medial wall of the hemisphere and has undoubtedly been removed in part in all previous ablation studies of the "premotor" area. Its removal was undertaken as an initial operation in 50-79 and as the only ablations in 50-149 (Fig. 2). Removal of face and arm subdivisions of this motor field is not too difficult, but ablation of the leg portion in its entirety without damage to the precentral leg area may be impossible.

A study of the serial sections of the brain of monkey 50-79 (reconstruction, Fig. 2), which, subsequently to the supplementary motor area lesions, had area 6 removed both dorsally and laterally in each hemisphere, shows the following

so far as the supplementary areas are concerned. On the right the arm area has been removed but the face and leg areas have been incompletely destroyed; there is no involvement of the precentral motor field. On the left, the arm and leg portions of the supplementary area have been destroyed, but in addition the lesion extends into the cingulate gyrus and there is considerable damage to the precentral leg area. It is probable that these unintended injuries occurred at the time of the supplementary area ablation rather than when dorsal area 6 was removed.

These animals were tested 9 and 16 weeks respectively after operation.

a. Results on the peanut slide test. Monkey 50-149 did not differ from the controls before or after operation (Fig. 5, curve 2). Monkey 50-79, which gave neurological evidence of involvement of the precentral motor area, showed considerable impairment in this test. His performance is charted in curve 3, Figure 5. (50-79 vs. normal: $t = 9.22$; df $= 33$; p. $< .001$)

b. Results on the problem boxes. Both animals showed the same type of difficulty, differing only in degree. The final speed of performance equaled the preoperative (Table I), but was achieved, apparently, only after a change in the preoperative pattern of solving the problem. They had great difficulty turning the crank past "12 o'clock". At this point they would start to move the crank back and forth. Finally they succeeded by using the fingers in rotating the proximal end of the crank after it had been lifted to the "12 o'clock" position. The difficulty obviously lay in an inability to make arm and shoulder movements necessary for turning the crank in the usual manner.

c. Results on the life-saver bar test. Monkey 50-149 performed as well as the control group. Monkey 50-79 was slower with his right hand than with the left (Table VIII).

2. Bilateral dorsal area 6. By dorsal area 6 we mean that portion of area 6 which lies between the medial edge of the hemisphere and the dorsal branch of the inferior precentral sulcus, rostral to the precentral motor area as defined by the stimulation experiments of Woolsey *et al.* (26). This corresponds approximately to Vogt's area 6 aβ as it extends on the dorsal aspect of the hemisphere and to Brodmann's original definition of area 6 in this region. In ablating dorsal area 6, cortex was removed to the bottom of the inferior precentral sulcus along its medial bank. Everywhere only the thickness of the cortex was removed in order to avoid damage to fibers leaving the supplementary motor area and to prevent damage to the precentral area. In the stimulation experiments dorsal area 6 yielded only pupillary dilatation at threshold intensities, while its unilateral ablation results in temporary pupillary inequality.

This area was ablated as described in 2 animals. It was removed bilaterally in 50-10 6 weeks after completion of bilateral precentral arm and leg lesions. At the same time most of the right frontal lobe rostral to the inferior precentral sulcus, including the orbital surface, was decorticated. Monkey 50-79 had dor-

sal area 6 removed bilaterally, 4½ months after the bilateral supplementary lesion was made.

Results. The animals were tested 7 to 8 weeks after operation. Neither of them showed any increased deficit on the *peanut slide*. Monkey 50-79, who had readapted to opening the *crank box* after his supplementary lesions, now performed as quickly as normals. Monkey 50-10 had his first retention test on the *crank box* after this operation. In the first six trials he was slower than the control group, but he improved his speed from 6 to 4 seconds per trial. He also learned to open the *slide box* and *combination box B* after this operation and did as well as two normal monkeys tested on these problems. Only 50-79 was tested on the *life-saver bar*. He showed improvement over his previous performance (Tables VII and VIII).

3. Lesions of dorsal area 6, variously combined with lesions of lateral area 6, frontal eye field, supplementary motor area and the rostral portion of the precentral motor area. With a view to removing all cortex that has been considered, "premotor", various lesions, more extensive than our "dorsal area 6", were made. To the supplementary and dorsal area 6 lesions of 50-79 was added bilateral removal of "lateral area 6". This corresponds approximately to the Vogts' areas 6 bα and 6 bβ, and includes cortex between the ipsilateral motor face area (26) and the sylvian fissure. The lesions in animals 49-4, 49-3, 49-2 and 49-1 are illustrated in Figure 3. In 49-4 the damage is mainly within dorsal area 6 and involves on both sides part of lateral area 6. In 49-3 the lesions extend about half way to the sulcus cinguli on both sides. They extend into the rostral third of the precentral motor area and into the frontal eye fields. The lesions in 49-2 also involve the precentral motor and the frontal eye fields. The ablation is more extensive in the right hemisphere and involves part of the supplementary motor area. Monkey 49-1 had much more of the precentral motor area ablated on both sides than any other animal of this group. Lateral area 6 was removed bilaterally, also most of dorsal area 6, and some of the adjacent medial walls. The frontal eye fields were less damaged.

Results. No additional impairment on the *peanut slide*, *latch boxes* or *life-saver bar* was produced in 50-79 by removal of lateral area 6. Monkey 49-4 was tested on the *pull box*, the *crank box*, the *hook and handle box* and on *combination box A* one month after operation. No change from his preoperative status was detected (Tables I, II, III). Likewise there was no change in monkey 49-3 when he was tested one month postoperatively on the *slide box*, the *ring box*, the *hasp box* and *combination box B* (Tables V, VI).

One month after operation 49-2 opened the *pull box* immediately but he had great difficulty operating the *crank box*. When the crank reached "1 or 2 o'clock" he kept moving it back and forth for one-half to one minute before it was carried beyond this point. This problem remained unchanged for 21 trials. Training was postponed for one month. At this time performance was

greatly improved and he reached the minimal time of 4 seconds (Table I). With the *hook and handle box*, at one month postoperatively, he required 31 trials to reach uniform performance. He was apparently too slow to work both the hook and the handle with the left hand, so he began using the right hand to lift the handle. At most trials, however, the right hand dropped the handle before the left drew the hook. Eventually both hands were coordinated well enough to enable him to open the box in 5 seconds. Once he had readjusted to the crank and to the hook and handle boxes he was able to open *combination box A* with the same speed as before operation.

Monkey 49-1 was tested on the slide, ring, hasp and combination B boxes one month after operation. He required more trials on the *slide box* than before operation (Table V). During retraining he continually moved the slide first in one direction, then in the other. He finally achieved his preoperative speed. He performed on the *ring box* as well as before operation. With the *hasp box* he changed his pattern of movement. Instead of moving the wooden plug toward the right with his right hand he moved it up and down until it fell out. In the *combination box* he was able to operate the slide and the ring but could not remove the plug from the staple. These were placed on the end of the box and the plug had to be moved away from the animal. This he could not do. When tested a month later he succeeded but required a larger number of trials than preoperatively.

C. Precentral and Supplementary Motor Area Ablations

Two monkeys were carried to this stage after having their precentral arm and leg area removed gradually. As has already been noted, 50-3 had considerable damage done the supplementary motor areas when the precentral leg areas were ablated. At the last operation destruction of the supplementary areas was completed without removal of dorsal area 6. Monkey 50-10 had already had the right orbitofrontal area and dorsal area 6 bilaterally removed in addition to the precentral arm and leg areas (Fig. 1). The animals were tested 9 weeks after these operations.

a. Results on the peanut slide test. These are charted in curve 5, Figure 5. Although both animals were already very defective in this test they now appeared slightly worse. The difference, however, may not be significant ($t = 2.20$; $df = 18$; $p. = 0.03$).

b. Results on the problem boxes. The animals were well oriented to these boxes. They opened the *pull box* immediately. They were unable to open the *crank box* in four successive daily sessions of one hour each. Although they tried, they were never able to lift the crank higher than "10 o'clock", but if the crank was set at "3 o'clock", they were able to pull the crank and release the lid immediately. It was clear that the difficulty was related to the posture from which they tried to lift the crank, to the greater impairment of motor control and to the

marked spasticity which these animals exhibited. Monkey 50-10 was able to work the *slide* and *combination B* boxes. In 9 trials he reached an optimum of 2 seconds on the slide box. In the combination box he was slower than after the precentral and dorsal area 6 ablations (Tables V and VI).

c. Results on the life-saver bar test. In carrying out this test 50-3 stood up (others remained seated). She placed one hand on the bar near the post and grasped the candy and bar with the other hand. In this fashion she displaced the candy while using the bar as support. The roles of the two hands were reversed when the bar was reversed. Both animals were slower than after precentral ablation. The decrease in speed was less in 50-3, who had lost part of the supplementary area at a previous operation (Table VIII).

D. Ablations of Somatic Area II, Temporal Lobes and Orbitofrontal Cortex

An initial bilateral removal of *somatic area II* on the dorsal bank of the sylvian fissure (24) was made in monkey 50-150 (Fig. 2). No neurological deficit followed this operation and no impairment of performance on peanut slide, problem boxes or life-saver bar was detected.

Neocortex of both *temporal lobes* was then removed to the extents shown in Figure 2. Striking behavioral changes occurred immediately, similar to some of those described by Klüver and Bucy (14) after temporo-hippocampo-amygdalal removal. The animal showed marked "oral tendencies". He would smell and taste all objects offered him. He was definitely tamer. Gradually his behavior became more normal, but his "oral tendencies" continued for the three months he was kept.

In spite of these marked behavioral changes this animal showed no deficits on the peanut slide, the problem boxes or the life-saver bar 15 days after the temporal lobe ablations.

Later the *orbitofrontal cortex* was removed bilaterally as shown in Figure 2. Immediately after operation there was a great increase in general motor activity which persisted. His neurological status was normal. In about 15 days he seemed even more tame than after the temporal removals. He was more indifferent to events about him than normal monkeys and did not engage in chattering and monkey play with the other animals. However, he noticed any object offered and continued to show "oral tendencies."

In the testing cage, 4 and 6 weeks after operation, he paced continuously. His performance with the crank box was definitely below his ability before the orbitofrontal ablation (Table I). However, the pattern of movement was the same and his performance was accurate and smooth. But he never stopped to turn the crank in a single movement. The hook and handle box was opened two hours after it was presented and he did not do better on two additional trials. After two months he returned to his preoperative performance. He failed to open combination box A and the push-pull was not opened except when rod 4

alone was set. It seemed that the more complex the problem, the less likely he was to finish it. After two months his performance with the crank, hook and handle and push-pull boxes improved remarkably.

Monkey 50-10 was deprived of his left orbitofrontal cortex after previous removals of the precentral, dorsal 6, supplementary areas and the right orbitofrontal cortex. No hyperactivity ensued in this case, possibly because of his previous motor ablations, but he seemed indifferent and more passive than before and did not make threatening movements. He became very silent and failed to engage in chattering with the other monkeys.

When tested one month after operation his status had altered. He was able to do as well (or as badly) as he had before the second orbitofrontal area had been removed.

DISCUSSION

A. Precentral motor area ablations. In the retention of motor habits after precentral ablations our results agree with the previous studies of Lashley (16) and of Jacobsen (11). On some of the latch boxes performance was comparable to that of normal monkeys. In others they differed from normals in the total number of trials required to reach uniform performance or in the minimal time required to execute the task. The degree to which precentral animals were able to compensate for their motor deficits varied with the task and with the relative motor deficits of right and left hands and with their success in substituting new movement patterns. One animal failed completely on the push-pull box. This apparently resulted from difficulty in using his hands in the trial and error fashion with which other animals tackled this problem, and from his inability to substitute another procedure as a consequence of the lack of insight into the problem which he shared with all monkeys.

Monkey 50-74, with an uncomplicated precentral ablation, did not show further impairment of arm function on removal of the leg areas, and one may conclude that the leg areas do not contribute to arm function. This agrees with the lack of any real overlap revealed by threshold electrical stimulation (26) and with the fact that no arm movements were obtained in this animal on stimulation of the leg area after complete ablation of the arm area at the previous operation.

Monkey 50-3 was outstanding among the precentral animals for her poor performance on the crank box. This is correlated with damage to the supplementary motor area, which in this animal was severe. The supplementary leg area was removed, and the arm portion was doubtlessly damaged. Her performance on the problem boxes and life-saver bar was intermediate between a precentral and a complete precentral-supplementary preparation (see below).

All precentral animals showed extreme impairment of their ability to catch rolling peanuts. Partial damage to the supplementary area did not seem to add

significantly to the difficulty. Failure of these animals to improve their performance at the peanut slide is in contrast with their achievements with the latch boxes and the life-saver bar. The difference appears to be that the peanut slide provided a continuously moving stimulus and required more precise motor performance in temporal and spatial dimensions. A fraction of a second too long taken in a movement means failure to catch the peanut. In the problem boxes it may simply mean a longer time per trial, or the deficiency may be unnoticed because of an inadequate timing system. A similar slowness in executing fine movements of the fingers was determined by Travis (18) by measuring the speed with which these animals picked up raisins from a board. Though in this case the raisins were stationary, their size required accurately directed movements. Both these tests require finer motor control than do the problem boxes and for this type of control the precentral motor area is apparently necessary. There is no evidence in any of the tests that the precentral area is requisite for any intellectual function which might have been required for the performance of the tests.

B. On the concept of a premotor area as a center for the elaboration of skilled movements. We have examined the question whether the so-called premotor cortex is essential for the retention and performance of learned skilled movements, defining as skilled movements the animal's ability to learn to operate problem boxes such as have been used in similar previous studies. We have failed to find that all or any portion of the cortex, variously described as premotor, intermediate precentral, area 6 or area FB, is essential for the retention of these movements. The supplementary motor area, which is on the medial wall of the hemisphere and occupies at least a portion of the cortex which has been called premotor, plays a role in motor performance but, as yet, it can scarcely be considered an "association area" or an area for "higher order" motor controls. With lesions of this area (50-79 and 50-149) there was difficulty in operating the crank box, but the difficulty seems readily accounted for by the impairments of movement and posture and by the spasticity which resulted from these lesions.

Removal of dorsal area 6 (as defined on p. 437) had no effect upon motor performance either when added to previous supplementary (50-79) or precentral (50-10) ablations or when made with minimal involvement of adjacent parts of the cortex (49-4 and 49-3). Nor did additional ablation of lateral area 6 (50-79) have any effect. When "premotor" lesions also caused considerable damage to the precentral motor area and to the adjacent supplementary motor area (49-2 and 49-1) impairment of performance on the tests was noted, but only during the period when there was considerable motor deficit. Similar but more marked deficits were noted following complete ablation of supplementary and precentral motor areas (50-3 and 50-10). There seems little doubt that the difficulties of performance which these animals exhibited can be attributed to

the neurological deficits of paresis, spasticity and postural adjustment which were present. They were always well oriented to the problem and showed no detectable evidence of an intellectual deficit. Even after complete bilateral removal of most of the cortex of the frontal lobe (50-10) deficit was not greater than after precentral plus supplementary ablations.

A factor of importance in the results of postoperative tests in this study, as compared with others, was the fact that more time for recovery of residual motor ability was allowed.

In one animal (50-150), with marked hyperactivity which developed after bilateral removal of orbitofrontal cortex, there was striking impairment of performance in simple problem boxes and complete failure to open more complicated ones. Nevertheless he greatly improved and two months after the operation he finally succeeded in opening even the most complicated box, the push-pull. If the temporary deterioration of the motor performance in 50-150 was actually due to the hyperactivity which resulted after the orbitofrontal lesion, it would be of interest to determine whether the poor performance on the delayed response test of the orbitofrontal preparation could be influenced by removal of the motor areas.

It is of interest to note that 50-150, as a temporal lobe preparation, performed all the tests in a fashion comparable to normal animals. Klüver (14) and Chow (5) have demonstrated, on temporal monkeys, great impairment of retention of visually mediated habits. The problem boxes are visual-kinesthetic-motor problems. Nevertheless we failed to find any deficit in this preparation. This observation is in agreement with Klüver's (15) results on a baboon with temporo-hippocampo-amygdalal removal. This animal had great difficulty in discriminating between a circle and a square but he could still solve a multiple stick problem.

SUMMARY

1. The relation of the "premotor" area to the retention and performance of learned skilled movements has been reexamined through study of 6 normal and 11 experimental monkeys.

2. The results have been related to recent findings on localization in precentral and supplementary motor areas and to the neurological deficits produced by ablating these areas.

3. Analysis of the results fails to support the concept of a premotor area especially concerned with the elaboration and retention of skilled movements.

4. All deficits produced could be accounted for on the basis of neurological disturbances resulting from injuries to the supplementary and the precentral motor areas. No deficit of skilled movements could be ascribed to lesions of area 6 apart from involvement of the supplementary and the precentral motor fields.

5. After bilateral precentral removal of arm and leg areas the animal shows striking failure in ability to pick up small moving objects. However, he retains ability to operate simple and complex problem boxes. On some of these his performance is as good as that of normal animals; on others performance is slowed.

6. After supplementary motor area lesions the animals were especially handicapped on the crank box, apparently because of impaired movements and spasticity in the proximal parts of the limbs.

7. With combined lesions of precentral and supplementary motor areas the animals were severely handicapped by disturbances of posture, difficulties of movement and spasticity. Performance was slower than after the precentral lesions but the animals remained correctly oriented toward the problems and failed only on the crank box.

8. No further deficit was produced by extending the lesions to include all of area 6 or most of the cortex of both frontal lobes.

9. No deficits were found after lesions of somatic area II and the temporal neocortex.

REFERENCES

1. AKERT, K. AND WOOLSEY, C. N.: Ventrolateral nuclear group of the thalamus and its projection upon the precentral motor cortex of the monkey. Fed. Proc., 1954, **13:** 1.
2. BRODMANN, K.: *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* J. A. Barth, Leipzig, Germany, 1909, xii, 324 pp.
3. BUCY, P. C.: Electrical excitability and cytoarchitecture of the premotor cortex in monkeys. Arch. Neurol. Psychiat., Chicago, 1933, **30:** 1205.
4. CAMPBELL, A. W.: *Histological Studies on the Localisation of Cerebral Function.* Cambridge University Press, New York, N. Y., 1905, xx, 360 pp.
5. CHOW, K. L.: Effect of partial extirpations of posterior association cortex on visually mediated behavior in monkeys. Comp. Psychol. Monogr., 1951, **20:** 187.
6. CRAWFORD, M. P., FULTON, J. F., JACOBSEN, C. F. AND WOLFE, J. B.: Frontal lobe ablation in chimpanzee: A résumé of "Becky" and "Lucy". Res. Publ., A. Nerv. & Ment. Dis., 1948, **27:** 3.
7. ECONOMO, C. VON AND KOSKINAS, G. N.: *Die Cytoarchitectonik der Hirnrinde des erwachsenen Menschen.* J. Springer, Vienna, Austria, 1925, 810 pp., atlas with 112 pl.
8. HORSLEY, V. AND SCHAEFER, E. A.: A record of experiments upon the functions of the cerebral cortex. *Phil. Tr. Lond.* 1888, **179B:** 1.
9. JACOBSEN, C. F.: A study of cerebral function in learning. The frontal lobes. J. Comp. Neurol., 1931, **52:** 271.
10. JACOBSEN, C. F.: The influence of extirpation of the motor and premotor areas of the cortex upon the retention and execution of acquired skilled movements in primates. Am. J. Physiol., 1933, **105:** 58.
11. JACOBSEN, C. F.: The influence of motor and premotor area lesions upon the retention of acquired skilled movements in monkeys and chimpanzees. Res. Publ. A. Nerv. & Ment. Dis., 1934, **13:** 225.
12. JACOBSEN, C. F., WOLFE, J. B. AND JACKSON, T. A.: An experimental analysis of the functions of the frontal association areas in primates. J. Nerv. & Ment. Dis., 1935, **82:** 1.

13. KENNARD, M. A., VIETS, H. R. AND FULTON, J. F.: The syndrome of the premotor cortex in man: Impairment of skilled movements, forced grasping, spasticity and vasomotor disturbances. Brain, 1934, **57:** 69.
14. KLÜVER, H. AND BUCY, P. C.: An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to "psychic blindness". J. Psychol., 1938, **5:** 33.
15. KLÜVER, H.: Personal communication, 1951.
16. LASHLEY, K. S.: Studies of cerebral functions in learning. The retention of motor habits after destruction of the so-called motor areas in primates. Arch. Neurol. Psychiat., Chicago, 1924, **12:** 249.
17. PENFIELD, W. AND WELCH, K.: The supplementary motor area in the cerebral cortex of man. Tr. Am. Neurol. A., 1949: 179.
18. TRAVIS, A. M.: Neurological deficiencies after ablation of the precentral motor area in *Macaca mulatta*. Brain, 1955, **78:** 155.
19. TRAVIS, A. M.: Neurological deficiencies following supplementary motor area lesions in *Macaca mulatta*. Brain, 1955, **78:** 174.
20. TRAVIS, A. M. AND WOOLSEY, C. N.: Motor abilities of adult *Macaca mulatta* following bilateral precentral and supplementary motor area lesions. Am. J. Physiol., 1952, **171:** 774.
21. TRAVIS, A. M. AND WOOLSEY, C. N.: Motor capacities of monkeys after bilateral sensorimotor and total decortications. Abstracts of Communications, 19th Internat. Physiol. Cong., Montreal, 1953: 950.
22. TRAVIS, A. M. AND WOOLSEY, C. N.: Motor performances of monkeys after bilateral partial and total cerebral decortications. Am. J. Phys. M., In press, 1956.
23. VOGT, C. AND O.: Allgemeinere Ergebnisse unserer Hirnforschung. J. Psychol. Neurol., Leipz., 1919, **25:** 277.
24. WOOLSEY, C. N.: Patterns of sensory representation in the cerebral cortex. Fed. Proc., 1947, **6:** 437.
25. WOOLSEY, C. N. AND BARD, P.: Motor performance of an adult *Macaca mulatta* following bilateral removal of areas 4 and 6. Fed. Proc., 1943, **2:** 55.
26. WOOLSEY, C. N., SETTLAGE, P. H., MEYER, D. R., SENCER, W., PINTO HAMUY, T. AND TRAVIS, A. M.: Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. Res. Publ. A. Nerv. & Ment. Dis., 1951, **30:** 238.

THE EFFECT OF PREDNISONE IN THE TREATMENT OF REFRACTORY CARDIAC EDEMA

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Numerous reports are currently being published about the functions of the two recently synthesized steroids, prednisone (delta-1-cortisone) and prednisolone (delta-1-hydrocortisone). On a weight basis they have been shown to have therapeutic potencies at least three times greater than their respective analogues, cortisone and hydrocortisone. More significantly, a very major advantage of the new agents over their precursors lies in their markedly diminished tendency to cause potassium depletion, sodium retention, edema, or hypertension (1, 2).

Such lack of cortisone-like effect on electrolytes was consistently observed in the course of a clinical investigation regarding the indicated use of prednisone[3] for diverse disorders among twenty-nine patients. Three of them, with compensated heart disease, developed no semblance of edema during or after treatment. Furthermore, of thirteen who had associated cardiac edema, eleven surprisingly recorded significant diuresis and weight loss within the first four to seven days of taking the new steroid.[4]

Thus, the case studies not only demonstrated that the drug could possess the expected advantage of *prophylaxis* against fluid retention, but they also suggested that it might have some *therapeutic* value toward diminution of preexisting cardiac edema. It is interesting to note that Camara and Schemm (3) recently obtained somewhat similar negative water balance following the use of the more hazardous sodium-retaining corticotropin in some cases under treatment for congestive heart failure.

This therapeutic concept regarding prednisone-induced diuresis might have been more valid if the agent had been employed entirely in decompensated cases which appeared to offer no indications for management with corticosteroids. Similarly, that fact was not considered in the series of Camara and Schemm, which actually included eight patients with rheumatic heart disease. It was therefore decided to try prednisone as an adjunct in the treatment of a hopelessly refractory cardiac patient who had no known indication for adrenal-steroid therapy.

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[3] The drug for this investigation was furnished as Meticorten® by the Schering Corp., Bloomfield, N. J.

[4] Tabulated data pertaining to the cardiac cases may be furnished on request.

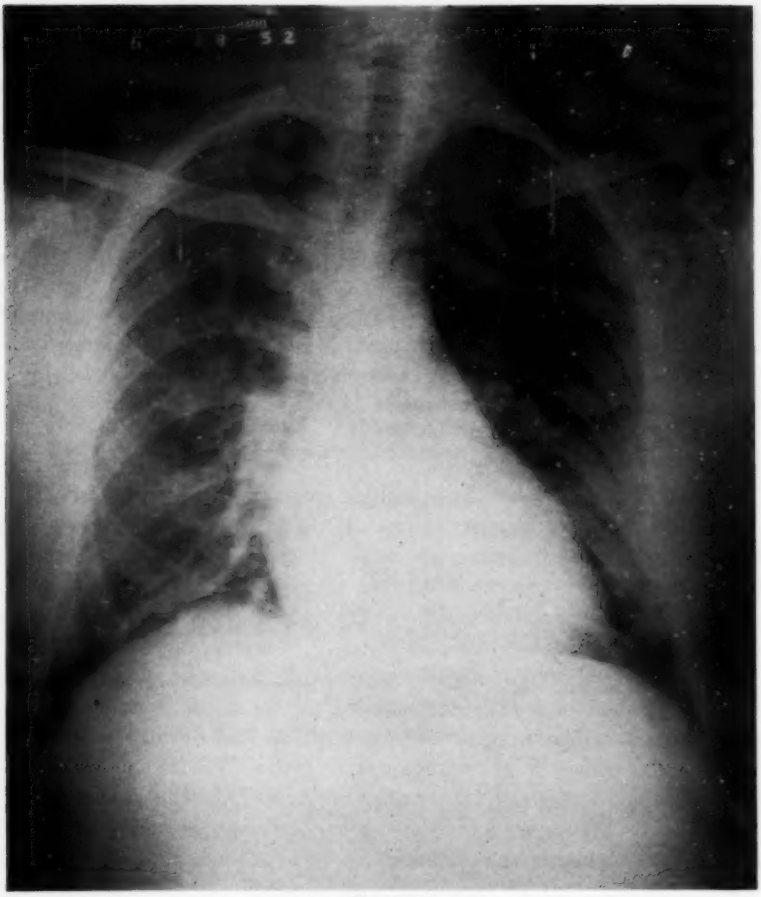

FIG. 1a

FIG. 1. Comparison of cardiac silhouettes.

(a) 5–28–52, when decompensation was first evident.

(b) 5–2–55, after patient had become completely refractory, just prior to the institution of prednisone therapy.

Note the marked increase of heart size, with prominence of right atrium, three years after the beginning of congestive failure.

CASE REPORT

J. P.—The patient is a 47-year old white male who, on April 9, 1943, at age 34, suddenly experienced excruciating substernal pain radiating down his left arm. No abnormal physical signs were found, but the electrocardiograph findings led to the diagnosis of acute posterior myocardial infarction. Numerous previous examinations had never revealed hypertension, signs or symptoms of rheumatic fever, or any other vascular disorders.

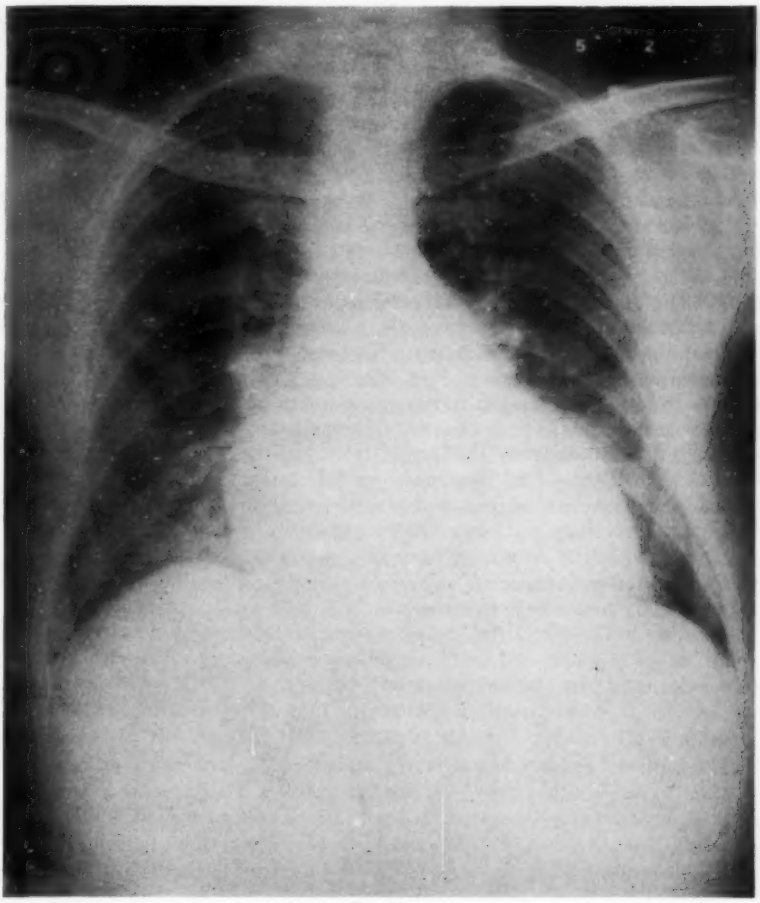

FIG. 1b

Subsequently recurrent attacks were recorded in December 1945, April 1946, and January 1952. The respective electrocardiograms were interpreted as showing acute posterior infarction, posterior wall damage of undetermined age, and superimposed acute anteroseptal injury. For each event he was hospitalized and treated by standard measures. At none of those times was he found to have any murmurs, arrhythmias, or signs of decompensation.

Eventually, on May 17, 1952, he suffered his severest attack, and then for the first time he showed evidence of cardiac dilatation and decompensation. There were cyanosis, dyspnea, and hemoptyses of frank blood. The heart was slightly enlarged to the left (see X-ray of May 28, 1952 in Fig. 1), there was a periodic protodiastolic gallop rhythm, and a harsh grade II systolic murmur was audible at the apex. The neck veins were engorged, there were coarse moist rales and wheezes throughout both lungs, and the liver edge was barely palpable. Serial electrocardiograms taken a few days apart were bizarre. In all of them the

rhythm alternated back and forth between normal sinus conduction, multifocal premature ventricular contractions, fusion beats, and all three degrees of A-V block. In succession the tracings demonstrated rapid change from left bundle branch block to normal intraventricular conduction, to arborization block, to right bundle branch block. The patterns respectively suggested electrical disappearance of infarction changes, ventricular aneurysm, lateral extension of anterior wall damage, and finally reappearance of the residual posterior wall infarct.

Treatment consisted of bed rest in semi-Fowler position, sedation, oxygen, slow digitalization, low salt diet, daily orange juice, ammonium chloride, mercuhydrin injections, and quinidinization despite the intraventricular conduction defect. Compensation, regular rhythm, and disappearance of all abnormal signs resulted within two weeks. On maintenance of the diet, digoxin 0.25 mg. twice daily, and quinidine 180 mg. four times daily, he was steadily tapered from all other therapy and was able to undertake a sedentary occupation three months later. With that regime he remained comfortable for eight months, requiring only a rare injection of mercurial.

However, by April 1953 congestive failure had recurred, and the patient was becoming progressively resistant to more frequent and larger doses of "primed" mercuhydrin even when administered intravenously. On May 24, 1953 mercurials were abandoned and he was given one 250 mg. tablet of acetazolamide[5] on five successive mornings per week. This resulted in prompt diuretic response and return of compensation. However, to maintain the effect it was necessary to increase the dose gradually to two, and occasionally three, tablets on each of the five mornings. After four months of success, peripheral edema appeared and progressed. A change to ammonium chloride and frequent mercuhydrin injections for a period of one month were of no avail.

Examination on October 11, 1953 revealed moderate enlargement of heart to right and left, return of apical systolic murmur, fine rales in lung bases, tender liver edge 3 cm. below costal margin, and 2 plus edema of ankles and lower legs. Laboratory tests showed: Serum sodium 138 meq./l., serum potassium 4.51 meq./l., 24-hour urine chlorides 5.82 gms., urine pH 6.5 with no abnormality of the filtrate, BUN 24 mg. per cent, RBC 3,840,000, hemoglobin 11.5 gms., and cephalin flocculation 3 plus. Some of the data seemed to be consistent with a late hypochloremic type of low salt syndrome. Temporary abandonment of all diuretics, slight increase of dietary salt, and profound bed rest brought about only a modicum of relief. After two weeks of that schedule, he was treated with pendulum alternation of "primed" mercuhydrin for three days followed by Diamox® for three days of each week; this program resulted in marked diminution of peripheral edema. However, it was necessary to increase the dosage of both drugs. By such means, comfort and capacity for light work persisted for almost one year.

In January 1955 the leg swelling became worse and was accompanied by pulmonary edema with marked orthopnea. Resumption of strict rest and of oxygen did not promote any diuresis. Periodic short courses of ferrous sulphate always overcame the mild anemias, but the elevated red blood cells never benefited the situation. Mictine, and later urea, were tried but were quickly abandoned because of ineffectiveness and the creation of severe nausea. A one-week trial with combined Diamox® and ammonium chloride was also of no value. Again the pendulum treatment with three days of mercuhydrin followed by three days of Diamox® was undertaken. Despite periodic administrations of the former intra-

[5] Acetazolamide was furnished as Diamox® by Lederle Laboratories, Pearl River, New York.

venously and increase of the latter to occasional levels of 1250 mg. per morning, the patient became steadily worse. He obtained relief only from chair sitting and use of bedside oxygen.

Examination on April 22, 1955 showed extreme generalized failure. There were dyspnea in the sitting position, cyanosis, marked engorgement of neck veins, further enlargement of heart to right and left (see X-ray of May 2, 1955 in Fig. 1), all heart sounds muffled but with gallop rhythm at apex, a grade II rough apical systolic murmur, a grade II softer systolic murmur just to left of xyphoid—intensified by inspiration, blood pressure of 80/70, regular pulse of 88, coarse rales in extreme lung bases, tender systolically pulsating liver 5 cm. below costal margin, palpable spleen 2 cm. below costal margin, distended abdomen with shifting dullness and fluid wave, 2 plus edema over sacrum, and 4 plus edema over entire elephantiasis-like legs. The electrocardiogram showed persistence of marked right bundle branch block. It was evident that the patient had increased cardiac dilatation with relative tricuspid insufficiency and anasarca. A twelve-day hospitalization for absolute rest, better oxygenation, continuation of maintenance digitalis and quinidine, and diminished use of diuretics failed to bring about any improvement. Oliguria persisted. With the increasing refractoriness to all therapy, the patient was considered to be in a terminal stage.

Because of the previous observations in cardiac cases that diuresis generally followed the use of prednisone, administration of that agent was begun on May 16, 1955 in the small dose of 2.5 mg. three times daily. There was an immediate increase of urine output, which became especially pronounced after injections of previously ineffective mercuhydrin. The volume went as high as 8600 cc. in a 24 hour period. The early factual data pertaining to diuresis before and after use of prednisone are graphically demonstrated in Figure 2. Concomitantly with the loss of edema, there was a steady diminution and eventual disappear-

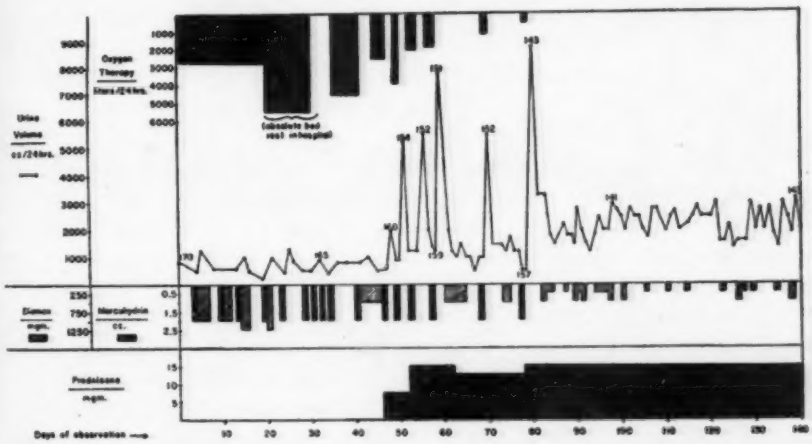

FIG. 2. Case J. P. Data pertaining to diuresis just before and after the addition of prednisone. The first day of record was April 1, 1955. The need for oxygen therapy was clinically parallel to the degree of pulmonary vascular congestion. Significant peak body weights are indicated numerically as pounds along the curve of urine volume. Mercuhydrin injections were usually "primed" by ammonium chloride. For additional details and for the results of continued observations, see text of case report.

ance of all signs and symptoms referable to the myocardial failure. By the 32nd day after starting the new drug, the patient had no rales, dyspnea, cyanosis, hepatosplenomegaly, ascites, peripheral edema, hypotension, muffled tones, murmurs, or gallop rhythm. The decreasing use of oxygen was by then completely abandoned.

He had recovered sufficiently to return to full-time light work on the 60th prednisone day. By January 20, 1956, the 250th day of continuous prednisone, he continues treatment with maintenance digitalis, quinidine, prednisone, and low salt diet with added potassium chloride and increased protein,—but he does not require oxygen. He takes no diuretics other than 250 mg. of Diamox® approximately twice weekly, and his urine output averages 1600 cc. per 24 hours. His daily weight averages 144 pounds. Although his electrocardiogram is unchanged and his cardiac silhouette still shows no diminution of size, he clinically remains well compensated, and he has progressively increasing tolerance for work.

DISCUSSION

The decision to try the addition of prednisone to the treatment of this case with refractory anasarca was based primarily upon the observation that the same steroid had appeared to induced diuresis in others with cardiac edema. Initially there was some trepidation that the drug could contribute to harmful breakdown of scarred tissue in healed areas of the patient's myocardium. However, that was overcome essentially by the revelation that previous controlled studies with the use of cortisone for experimentally created myocardial infarcts had failed to show any aggravation of the induced cardiac pathology (4, 5).

Any attempt to explain the dramatic response in the detailed report of patient J. P. must include consideration of many physiologic facts already reported or discussed in the voluminous literature about the functions of adrenal cortico-steroids. These may be grouped ito (a) direct effect on myocardium, (b) extra-cardiac benefits contributing to improvement of cardiac function, and (c) effects tending to create diuresis.

In the first category, Dorfman (6) making comparative animal studies of the several biologically active adrenal steroids, showed that only hydrocortisone and cortisone produced high and significant effects on glycogen deposition and muscle work capacity; prednisone was not then available for inclusion in the experiments. Goodman and Gilman (7) indicate that the steroids may improve muscle function by mobilization of glucose for energy rather than by any specific effect on electrolytes; this is in keeping with the clinical experience that the steroids under discussion are superior to desoxycorticosterone for overcoming the asthenia of Addison's disease. The implication here is that cardiac muscle could have the same responsiveness as the structurally and biochemically similar striated muscle studied in the aforementioned reports. Finally, because of the well-known ability of adrenal steroids to alter collagen tissue, it should be realized that myocardial infarcts tend to be organized with the formation of collagen (8), and that drug-induced dissolution of such excess fibroblastic reactivity might possibly allow better contractility of heart muscle fibers.

In the second group, there are several extra-cardiac responses which could indirectly offset impairment of cardiac function. First, the usual tendency of the drug to create euphoria and increased appetite often promotes general or apparent clinical improvement in many critical situations. More specifically, the cortico-steroids can stimulate erythropoiesis when anemia exists (1), and with it there could result an increase of oxygen-carrying capacity for better nourishment of an ischemic heart. Also the frequency of corticogenic hypothyroidism has long been known (9), and it is now generally accepted that lowered metabolism can decrease the work load for patients with advanced heart disease. Lastly, the adrenal steroids can help overcome impaired pulmonary ventilation. The most recent publication on the subject is that of Bickerman, *et al.* (10) who employed prednisone for the treatment of pulmonary fibrosis. It is interesting that they coincidentally observed significant diuresis in three cases of cardiac insufficiency which had not been treated with previous cortisone. They attributed the water loss solely to the relief of hypoxia, and they presumed that diuresis would not occur if there be normal diffusion of oxygen from lungs to tissues. However, one cannot overlook the possibility that increased alveolar transport of oxygen could result in decreased burden to overtaxed or ischemic heart muscle, even in the absence of a pulmonary disorder.

Finally, most difficult to evaluate is the observed diuresis which is the major topic of this report. Many factors may be contributory. After administration of corticotropin to normal subjects, Earle and his co-workers (11) found elevation of glomerular filtration rates to account for increased excretion of urinary sodium and water. Additional suggestion of a direct renal effect arose from the creation of pronounced diuresis after administration of ACTH or cortisone in the treatment of the nephrotic syndrome (12, 13). However, extra-renal factors also had to be considered. Birnie, *et al* (14) found that the blood level of an antidiuretic substance in rats could not be elevated by adrenalectomy when cortisone was given. Forsham and Thorn (15) state that cortisone and hydrocortisone antagonize the water-retaining effect of posterior pituitary vasopressin. Based primarily on the hypothesis that adrenal cortex activation might inhibit a desoxycorticosterone-like antidiuretic agent, Camara and Schemm (3) courageously administered corticotropin to cases with resistant congestive heart failure. Not merely were their results similar to those experienced by nephrotics who had received the same drug, but they also made the surprising observation that some of the patients developed a restoration of diuretic response to previously ineffective mercurials.

Since the discovery of prednisone and prednisolone, the numerous reports about their variable and superior functions have not yet included any detailed study pertaining to their possible role in aiding diuresis. As previously indicated, that function appeared as a striking coincidence in the present series of

cases with associated edema. In an early report Kinsell, *et al.* (16) had mentioned in a footnote that after using the new drug, "sodium diuresis, rather than sodium retention may be encountered at times." In the same conference Seldin (17) stated that large doses of Meticorten®, in common with other adrenal steroids, can cause diuresis as a result of cellular breakdown which liberates increased potassium, sodium, chloride, and nitrogen in the urine. It is tempting, although premature at this time, to offer a theory regarding one possible mechanism that could lead to the diuretic effect. In some patients with heart disease there may be an excess of aldosterone in the urine, and when this is so, the kidney is retaining sodium and the body is accumulating edema fluid. In patients with nephrosis, the aldosterone output is decreased after treatment with ACTH or cortisone when the diuresis later ensues (18). It is herewith postulated that in some individuals with cardiac failure prednisone might act similarly, and that its increased potency might quickly suppress output of adrenal cortex steroids, the latter including an antidiuretic agent such as aldosterone.

Practically all of the factors listed in this discussion are at present unconfirmed or controversial, and they should not yet be accepted as actual explanations for the abolition of refractoriness to cardiac treatment. Nevertheless, the dramatic success following the use of prednisone as experienced in the above situations is at least thought-provoking. In most respects it conforms with the results of the earlier work done by Camara and Schemm along similar lines. However, it appears that prednisone should be safer, faster, and more reliable than the corticotropin they used. It is felt that the current findings merit investigation of the drug in a large number of well-selected cases, with adequate controls and with laboratory data pertaining to electrolytes, renal function, pulmonary ventilation, and hormone assays. Until then, the present data are offered merely as provocative observations.

SUMMARY

1. Prednisone, when used in a series of patients who had associated cardiac decompensation, not merely lived up to its expectations for preventing aggravation of the edema state, but it also seemed to promote beneficial diuresis.

2. Because of that finding, the apparently non-indicated drug was added to the treatment of a patient who had multiple myocardial infarctions and who had developed a hopelessly refractory anasarca. This was followed by immediate potentiation of diuretic medications, rapid loss of edema, and restoration of cardiac compensation.

3. The factors responsible for such a result may be numerous, but they are as yet merely speculative. It is suggested that the present observations alone warrant future extensive investigation regarding the possible value of prednisone in the management of some cases with refractory cardiac edema.

REFERENCES

1. Bunim, J., Pechet, M. and Bollet, A.: Preliminary observations on the antirheumatic potency, metabolic effects, and hormonal properties of metacortandralone and metacortandracin. Read at Interim Session of the American Rheumatism Association, Bethesda, Md., November 4, 1954.
2. Demartini, M., Boots, R., Snyder, A., Sandson, J. and Ragan, C.: Comparative effects of prednisone and cortisone. J. A. M. A. 1955, **158:** 1505.
3. Camara, A. and Schemm, F.: Corticotropin in heart disease: Its paradoxical effect on sodium excretion in resistant congestive failure. Circulation 1955, **11:** 702.
4. Johnson, A., Scheinberg, S., Gerisch, R. and Saltzlein, H.: Effect of cortisone on experimentally produced myocardial infarcts. Harper Hosp. Bull. 1951, **9:** 187.
5. Hepper, N., Pruitt, R. and Edwards, J.: Effect of cortisone on healing of experimentally produced myocardial infarction in dogs. Fed. Proc., 1953, **12:** 391.
6. Dorfman, R.: Bioassay of steroid hormones. Physiol. Rev., 1954, **34:** 138.
7. Goodman, L. and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, 2nd edition. The Macmillan Co., New York, N. Y., 1955, 1659–1660.
8. Gould, S.: *Pathology of the Heart*, 1st edition, Charles C Thomas, Springfield, Ill., 597–598.
9. Wolfson, W., Beierwaltes, W., Robinson, W., Duff, I., Jones, Jr., Knarpp, C., Siemienski, J. and Eya, M.: Corticogenic hypothyroidism. *Proceedings of the Second ACTH Conference*, Vol. II. The Blakiston Co., New York, N. Y., 1951, 95–121.
10. Bickerman, H., Beck, G., and Barach, A.: The use of prednisone (meticorten) in respiratory disease; pulmonary emphysema and pulmonary fibrosis. J. Chron. Dis. 1955, **2:** 247.
11. Earle, D., Alexander, J., Farber, S., and Pellegrino, E.: Observations on the relation of renal function changes to the electrolyte and glycosuric effects of ACTH. *Proceedings of the Second ACTH Conference*, Vol. I. The Blakiston Co., New York, N. Y., 1951, 139.
12. Farnsworth, E.: Metabolic changes associated with administration of adrenocorticotropin in nephrotic syndrome. Proc. Soc. Exper. Biol. & Med., 1950, **74:** 60.
13. Luetscher, J., and Deming, Q.: Treatment of nephrosis with cortisone. J. Clin. Invest., 1950, **29:** 1576.
14. Birnie, J., Eversole, W., Boss, W., Osborn, C. and Gaunt, R.: An antidiuretic substance in the blood of normal and adrenalectomized rats. Endocrinology, 1950, **47:** 1.
15. Forsham, P., and Thorn, G.: The adrenals, in *William's Textbook of Endocrinology*, 2nd edition, W. B. Saunders Co., Philadelphia, Pa., 1955, 235.
16. Kinsell, L., Michaels, G., Coelho, M., Foreman, N. and Friskey, R.: Metacortandracin and metacortandralone, comparative clinical and metabolic evaluation. Presented at the First International Conference on the Clinical and Metabolic Effects of Meticorten and Meticortelone, May 31, 1955.
17. Seldin, D.: The impact of Meticorten on water and electrolyte metabolism. Ibid.
18. Luetscher, J. and Curtis, R.: Aldosterone: Observations on the regulation of sodium and potassium balance. Ann. Int. Med., 1955, **48:** 658.

STAPHYLOCOCCAL ENTEROCOLITIS IN CHINCHILLAS[1]

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Pathologic lesions of the gut, consisting of shallow ulcerations and pseudomembrane formation have been described in association with a variety of human diseases. In recent years, however, interest has centered upon "pseudo-membranous enterocolitis" associated with overgrowth of the intestinal flora by pathogenic staphylococci (1, 2). This disease, manifested by profuse diarrhea and peripheral vascular collapse, often fatal, has been recognized with increasing frequency as a probable complication of the administration of various antimicrobial drugs, in particular the so-called "broad-spectrum" antibiotics (3). Several factors have been thought to play a part in the pathogenesis of this disorder, including abdominal surgery (4, 5), previous hypotension (6), and thrombosis of submucosal vessels (7). However, a consistent finding has been the presence of increased numbers of hemolytic staphylococci in the intestinal contents and these organisms have proved almost invariably to be resistant to the antibiotics that the patient had been receiving.

During investigations of an outbreak of fatal diarrheal disease in a commercial colony of chinchillas, the finding of multiple enteric ulcerations with pseudomembrane formation led to bacteriologic studies. It was demonstrated clearly that the lesions were associated with overgrowth of the intestinal flora by hemolytic *Staphylococcus aureus* in animals fed for many months on pellets containing chlortetracycline.

The present communication describes the bacteriologic and pathologic aspects of this disease in chinchillas as well as the results of certain therapeutic and preventive measures.

Background—The chinchilla (Fig. 1), valuable commercially for its fur, is apparently susceptible to a wide variety of diseases, few of which are well understood. Both diarrhea and obstipation are well-known to commercial breeders as hazards in these animals (8), but seldom have systematic investigations been attempted. Treatment or prophylaxis of enteritis has been largely empirical, based on supposed dietary factors or, frequently, suspected infection with enteric pathogens of the *Shigella*, *Salmonella* or *Pseudomonas* groups. Many protozoan and helminth parasites have also been described (8, 9).

The present study was carried out in a colony of about 450 chinchillas. According to the owners, more than 50 animals had died during the preceding 6

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FIG. 1. Healthy male chinchilla.

months with a characteristic symptom-complex. Previously healthy animals became lethargic, preferring to sit quietly with heads bowed, in striking contrast to their typical, alert attitude and almost constant activity. This was followed by refusal of feed and water and the development of diarrhea with frequent small liquid or semi-liquid stools, occasionally containing streaks of blood. Within 12 to 36 hours, affected animals became unresponsive, went into "shock" (as evidenced by cold ears and cyanosis of the mucous membranes), and died quietly.

This train of events was said to be well-known to other chinchilla breeders in the area and was referred to as "sudden death". It was not uncommon for apparently healthy animals to be found dead within a few hours with evidence of diarrhea as the only clue to etiology.

Further inquiry revealed that for the preceding 18 months the colony of animals under investigation had been fed a commercial pellet containing approximately 0.2 mg. of chlortetracycline per ounce. When questioned, the owners stated that "sudden death" with diarrhea had not been a problem before adoption of this dietary regimen. They further volunteered the information that shortly after the feeding of pellets of this type had begun, they had observed and commented upon the fact that the droppings of the majority of the animals in the colony had changed in character, becoming softer in consistency and blackish-brown instead of the usual olive-green or brown previously noted.

Post-mortem findings—During a period of two weeks, five animals in the colony developed typical manifestations of lethargy and diarrhea, refused to eat or drink, and died within 12 to 36 hours. Autopsies were performed on four of these animals and revealed strikingly similar findings.

With the exception of the presence of liquid fecal material in the gut, no

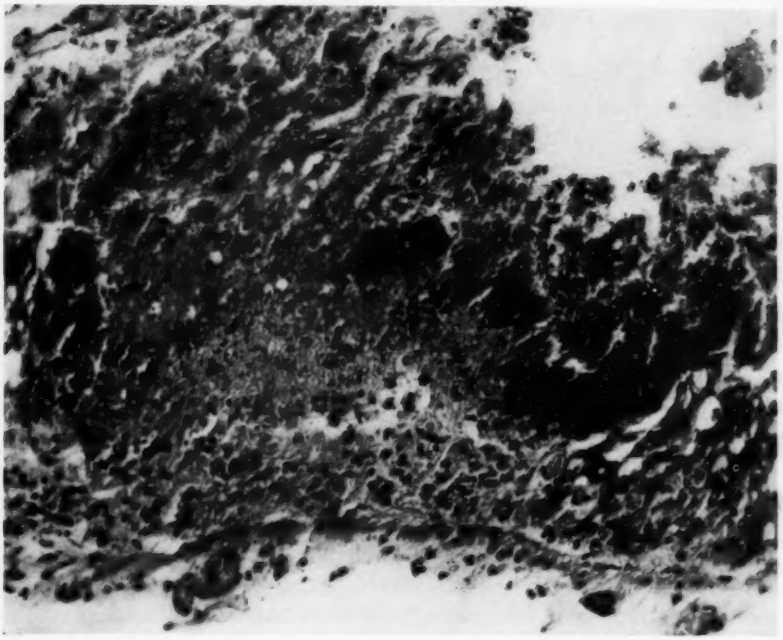

FIG. 2. Typical mucosal ulceration with overlying pseudomembrane in colon of chinchilla. Large clumps of cocci can be seen in the pseudomembrane. (Hematoxylin and Eosin, × 250).

gross abnormalities were present. Microscopic examination of histologic sections from the large intestine showed multiple areas of focal necrosis in the mucosa and shallow ulcerations covered by a pseudomembrane composed of fibrin, mucosal and inflammatory cells, many of which were degenerating, and mucus (Fig. 2). Similar, but less extensive, lesions were seen in occasional sections of small intestine. There were accumulations of polymorphonuclear leukocytes and many mononuclear cells in the submucosa, but none of the ulcerations extended beyond the lamina propria (Fig. 3). The muscularis and serosa were intact. The lesions corresponded closely to those observed in human cases of staphylococcal pseudomembranous enterocolitis (see Figs. 4 and 5). Bacterial staining of representative sections revealed myriads of Gram-positive cocci in huge clumps. In many areas, no Gram-negative bacteria could be found. No parasites or fungi were seen. There were no lesions of significance in the microscopic sections of lung, kidney, spleen, stomach, liver, adrenal and pancreas.

Bacteriologic findings in autopsied animals—Antemortem stool cultures from four animals and throat cultures from two were inoculated onto desoxy-

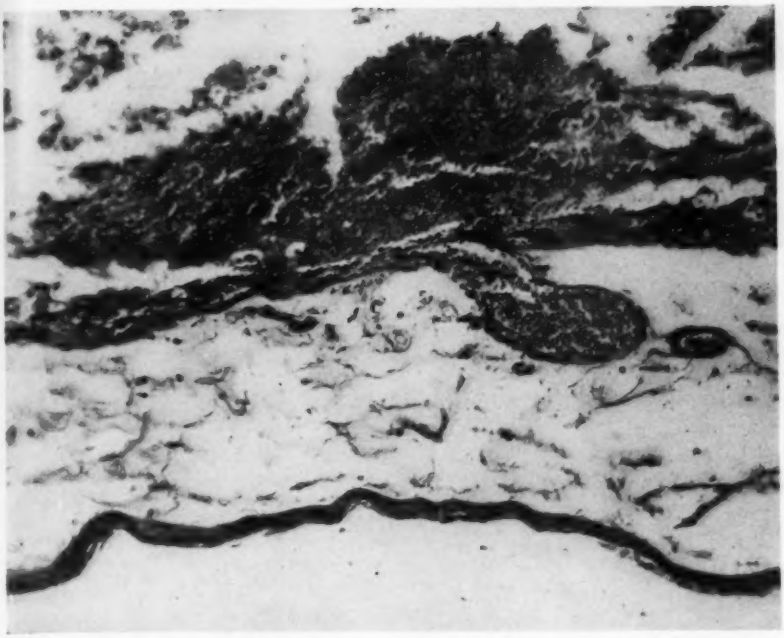

FIG. 3. Details of pseudomembrane covering mucosal ulcers in colon of chinchilla. (Hematoxylin and Eosin, × 150.)

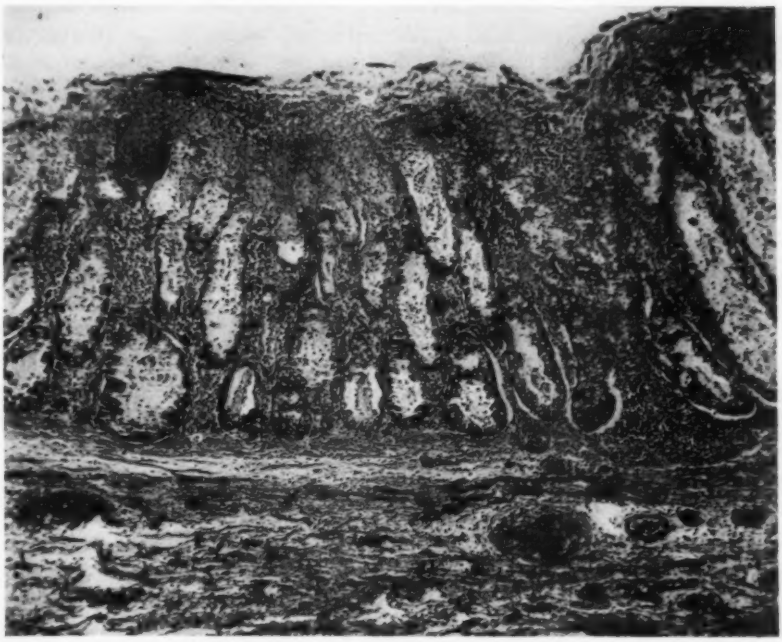

FIG. 4. Characteristic mucosal ulceration and pseudomembrane in a fatal human case of staphylococcal colitis that developed during treatment with multiple antibiotics (Autopsy No. 26180). (Hematoxylin and Eosin, ×60.)

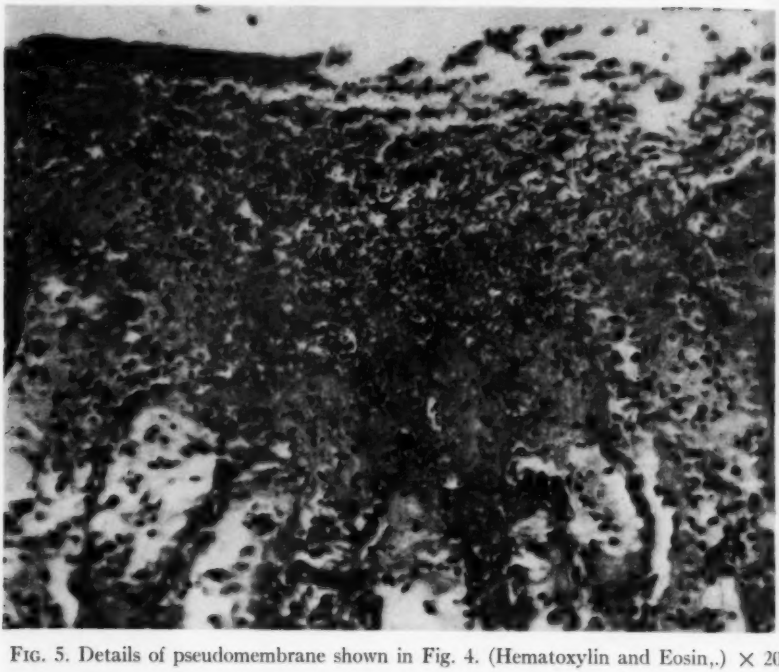

FIG. 5. Details of pseudomembrane shown in Fig. 4. (Hematoxylin and Eosin,.) × 200

cholate agar, S-S agar, blood agar and PEA (BBL) agar. All showed profuse growth of hemolytic *Staph. aureus* on blood and PEA plates. Although occasional colonies of *Proteus*, *Pseudomonas*, and enterococcus were seen, organisms of the coli-aerogenes group were rarely seen. From none of the fecal specimens were bacteria of the genus *Shigella* or *Salmonella* grown.

Post-mortem cultures of intestinal contents again showed almost pure growth of *Staph. aureus* from all animals. However, two cultures of heart blood and one from lung were bacteriologically sterile.

The results of cultural studies of these four animals are summarized in Table I, which includes the results of stool culture from the fifth animal that died, but was not autopsied.

Further observations, including therapy—On the basis of (a) the finding of intestinal ulcerations, pseudomembrane formation and Gram-positive cocci in histologic sections and (b) the recovery of *Staph. aureus* from intestinal and throat cultures, inquiry was made into the possibility that animals in the colony had ingested some antibiotic. Antibiotic medication of any type was at first denied by the owners, but further investigations revealed, as mentioned above, that for more than a year these chinchillas had been fed pellets containing small amounts of chlortetracycline.

TABLE I

Bacteriologic Findings in Five Animals Dying with Staphylococcal Enterocolitis

Animal	Sex	Age	Diarrhea	Cultures				
				Antemortem		Postmortem		
				Stool	Throat	Stool	Lung	Blood
		months						
F-1	F	14	Present	HSA	HSA	HSA	0	ND
F-2	M	6	Present	HSA	ND	HSA	ND	0
F-3	M	8	Present	ND	ND	HSA	ND	ND
F-4	M	6	Present	HSA	ND	HSA	ND	ND
F-5	M	4	Present	HSA	HSA	HSA	ND	0

Autopsy was performed on all animals except F-3.

HSA: Massive growth of hemolytic *Staphylococcus aureus* (occasional *Proteus, Pseudomonas,* enterococcus; rare coliforms). ND: Not done. 0: No growth.

Seven strains of staphylococci isolated from diseased animals were tested for susceptibility to a number of antibiotics using a "tube-dilution" technique. Aliquots of a diluted 18-hour broth culture of each organism were added to tubes containing serial dilutions of antibiotics in broth. The highest dilution showing no turbidity after incubation for 24 hours at 37°C. was taken as the "bacteriostatic" end-point. In addition, with four of the strains tested, cultures from tubes showing no turbidity were made on blood agar plates in order to establish a "bactericidal" end-point. The results of these studies are shown in Table II. All strains were sensitive to penicillin and erythromycin and some degree of susceptibility to neomycin and bacitracin was also evident. The results with tetracycline and chlortetracycline indicated resistance of a degree that would be considered therapeutically significant in only two instances.

With this information at hand the following regimen was adopted in an attempt to prevent the occurrence of "sudden death":

(1) All animals were changed to a diet of pellets of similar nutritional content containing no antibiotics.

(2) Antibiotics were added to all drinking water for a four-day period. The drugs used were neomycin in a concentration of 50 units/ml. and bacitracin, 25 units/ml. Because blood cultures had shown no growth and no evidence of systemic invasion by staphylococci was found at autopsy, it was felt that these drugs were suitable. Neither is appreciably absorbed from the gastrointestinal tract; both would be present in the gut in concentrations great enough to destroy most of the staphylococci present and, presumably, accelerate return of intestinal flora to normal.

Before institution of this program, rectal swab cultures were obtained from six normal animals and three with diarrhea of recent onset. Five days later, at the end of the period during which neomycin and bacitracin had been added to

TABLE II

Antibiotic Sensitivities of the Staphylococci Isolated from Intestinal Contents of Chinchillas with Diarrhea

Drug	Strains of *Staph. aureus*						
	S-1	S-2*	S-3	S-4	S-5	S-6	S-7
Penicillin (units/ml.)	0.5/0.5	0.2/1.0	1.0/250	0.2/0.5	1.0/ND	1.0/ND	0.5/ND
Erythromycin (mcgm./ml.)	0.5/20	0.2/50	0.2/100	0.2/10	1.0/ND	1.0/ND	0.2/ND
Tetracycline (mcgm./ml.)	0.2/50	0.2/100+	100/100+	0.2/20	5.0/ND	100+/ND	0.2/ND
Chlortetracycline (mcgm./ml.)	0.2/20	0.2/100+	50/100+	0.2/20	10/ND	100+/ND	0.2/ND
Chloramphenicol (mcgm./ml.)	20/100+	20/100+	10/100+	10/100+	10/ND	10/ND	10/ND
Bacitracin (units/ml.)	0.2/0.2	5.0/20	20/20	10/20	20/ND	10/ND	5/ND
Neomycin (units/ml.)	10/20	5.0/20	0.5/20	1.0/20	5.0/ND	5.0/ND	1.0/ND
Spiramycin (mcgm./ml.)	50/100+	20/100+	50/100+	20/50	50/ND	50/ND	20/ND
Amimycin (mcgm./ml.)	5.0/100	5.0/100+	5.0/100+	5.0/100+	5.0/ND	5.0/ND	5.0/ND
Streptonivicin (mcgm./ml.)	0.2/50	0.2/5.0	1.0/100	1.0/5.0	1.0/ND	0.2/ND	1.0/ND

Eighteen-hour broth culture of test organism diluted 10^{-3} and inoculated in tubes containing serial dilutions of antibiotics. After incubation at 37°C. for 24 hr., first tube showing no turbidity taken as "bacteriostatic" endpoint (shown as numerator). Tubes showing no turbidity were cultured on blood-agar for strains S-1 to S-4 and first dilution giving no growth taken as "bactericidal" endpoint (shown as denominator).

ND: Not determined.

* Strain S-2 was isolated from animal C-2 (Table III) before treatment.

TABLE III

Bacteriologic Findings Prior to and After Completion of Therapy with Neomycin and Bacitracin

Animal	Diarrhea	Stool Cultures		Remarks
		Before B	After B	
C-1	Present	HSA	NF	Diarrhea improved; survived
C-2	Present	HSA*	HSA†	Diarrhea improved slowly; survived; culture normal 20 days later
C-3	None	NF	NF	
C-4	None	NF	ND	
C-5	None	NF	ND	
C-6	Present	HSA	NF	Diarrhea improved; survived
C-7	None	NF	NF	
C-8	None	NF	NF	
C-9	None	NF	NF	

Animals received neomycin 50 units/ml. and bacitracin 25 units/ml. in drinking water for 4 days between cultures.

HSA: Hemolytic *Staphylococcus aureus* predominant. NF: Normal flora (mixture of coliform organisms and enterococci). ND: Not done.

* See strain S-2, Table II.

† This organism was resistant to 100 units/ml. of neomycin and bacitracin.

the drinking water, rectal cultures were again collected from four of the normal chinchillas and from all three with diarrhea.

As can be seen in Table III, hemolytic staphylococci predominated in cultures taken prior to treatment from the animals with diarrhea. In contrast, cultures obtained from well animals grew a mixture of Gram-negative bacilli, occasional enterococci, but no staphylococci.

After therapy, although diarrhea had almost subsided in the sick chinchillas, staphylococci persisted in large numbers in the stool of one (No. C-2). It is interesting to note that these organisms proved to be resistant to both neomycin and bacitracin in concentrations of 100 units/ml. All three of these animals survived and rectal swab culture obtained 20 days later from No. C-2 showed only normal flora.

Five days after completion of the course of neomycin and bacitracin, nine additional animals from the colony were cultured at random; in none were staphylococci isolated.

There were no evident ill effects from the administration of neomycin and bacitracin. For a number of days after the change in diet, occasional animals became constipated. This is apparently common among chinchillas and is quickly detected from the character of the droppings and by abdominal palpation. The administration of a laxative containing phenolphthalein was effective in relieving all cases.

Within one month, the stools of all animals reverted to an olive-green or brown color and were of firm consistency. At the time that this report was written there had been no recurrence of "sudden death" in the colony.

DISCUSSION

The fatal enterocolitis characterized by mucosal ulceration, pseudomembrane formation, and overgrowth of intestinal flora by hemolytic staphylococci observed in this colony of chinchillas bears a striking resemblance to the intestinal complications in some human subjects given antibiotics, particularly tetracycline derivatives.

A causal relationship of the small amount of chlortetracycline in the diet to the occurrence of intestinal lesions in these animals has not been established conclusively by the present study. However, several considerations render probable the conclusion that ingestion of this drug in tiny doses over a period of months brought about changes in intestinal microflora favoring multiplication of staphylococci.

(a) The abrupt termination of the disease in the colony when chlortetracycline was eliminated from the diet is noteworthy. This occurred despite failure of a brief course of bacitracin and neomycin to eliminate staphylococci from the stools of all animals (see animal C-2, Table III).

(b) Human cases of staphylococcal enterocolitis have been described after administration of antibiotics in "therapeutic" doses, levels that far exceed the

"nutritional" doses of these drugs now included in many types of domestic animal feed and in the pellets received by the chinchillas of this colony. However, the evidence accumulated from extensive studies indicates that beneficial effects on gestation, enhancement of growth, etc. observed in domestic animals given "nutritional" doses of antibiotics are due to "favorable" changes in intestinal flora resulting from the antimicrobial action of these drugs (10, 11). Furthermore, it is now well-recognized that the overgrowth of "unfavorable" microflora in certain environments can not only obviate expected benefits but, if pathogenic species multiply, can lead to the occurrence of frank disease when antibiotics are fed to animals (12). In this connection, two aspects of the feeding of antibiotics to chinchillas are of interest. Although experiences with other animal species make it reasonable to suppose that feeding antibiotics might be nutritionally beneficial in the chinchilla, the authors have been unable to find records of controlled studies of the effect upon growth, etc. of feeding these drugs in this animal. Secondly, in most domestic animals, antibiotics are fed for relatively brief periods to enhance early growth, to fatten for marketing, etc. In chinchilla raising, however, a majority of animals are kept year after year for breeding purposes and there is, as yet, no large annual turnover of marketable stock, so-called "pelters". This empirical practice of feeding antibiotics on a continuous, long-term basis may offer unusual opportunities for "superinfection" to occur.

A thorough search of published reports as well as communication with numerous laboratories of veterinary pathology and animal nutrition has failed to reveal any previous description of staphylococcal enterocolitis in animals. It is possible that the disease has occurred but has gone undetected because of the absence of macroscopic lesions or failure to employ proper cultural methods. On the other hand, the present authors may have been dealing with a unique situation in this chinchilla colony (such as the introduction of unusually virulent staphylococci into the environment at an inopportune time). A planned cultural survey of nasal flora among caretakers in this colony was abandoned when it was learned that the establishment was open daily to visits from the public.

Although another culturally proven instance of staphylococcal enterocolitis has recently been observed at autopsy in an animal from another chinchilla colony, also fed on pellets containing chlortetracycline, there are no data to indicate the true incidence of this disorder in these animals. It is entirely possible that the term "sudden death" has been applied by local breeders to a variety of diseases both before and after the practice of adding antibiotics to diets was begun. No systematic survey of chinchilla farms has been undertaken by the present authors and none is planned.

Finally, should production of this disease under controlled experimental con-

ditions prove to be feasible, the information obtained could be expected to have value in prevention or control of its human counterpart.

SUMMARY

The occurrence of pseudomembranous enterocolitis associated with overgrowth of intestinal flora by hemolytic *Staph. aureus* in chinchillas is reported. This is believed to be the first description of this disease in animals. Its striking resemblance to staphylococcal enterocolitis in humans after administration of antibiotics is pointed out. Reasons are cited for attributing the disease in chinchillas to the feeding of chlortetracycline in small amounts for "nutritional" purposes over a period of many months.

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REFERENCES

1. Kleckner, M. S., Bargen, J. A. and Baggentoss, A. H.: Pseudomembranous enterocolitis: Clinicopathologic study of fourteen cases in which disease was not preceded by operation. Gastroenterology, 1952, **21:** 212.
2. Terplan, K., Paine, J. R., Sheffer, J., Egan, R. and Lansky, H.: Fulminating gas-enterocolitis caused by staphylococci: Its apparent connection with antibiotic medication. Gastroenterology, 1953, **24:** 476.
3. Editorial: Antibiotics, staphylococci, and enterocolitis. New England J. Med., 1955, **253:** 201.
4. Penner, A. and Druckerman, L. J.: Enterocolitis as a postoperative complication and its significance. Gastroenterology, 1948, **11:** 478.
5. Dixon, C. F. and Weismann, R. E.: Acute pseudomembranous enteritis or enterocolitis: A complication following intestinal surgery. Surg. Clin. N. Amer., 1948, **28:** 999.
6. Penner, A. and Bernheim, A. I.: Acute postoperative enterocolitis. A study on the pathologic nature of shock. Arch. Path., 1939, **27:** 966.
7. McKay, D. G., Hardaway, R. M., III, Wahle, G. H., Jr. and Hall, R. M.: Experimental pseudomembranous enterocolitis. Arch. Int. Med., 1955, **95:** 779.
8. Brenon, H. C.: Postmortem examinations of chinchillas. J. Am. Vet. M. A., 1955, **126:** 222.
9. Hayes, F. A.: Parasitism in the chinchilla. Nat. Chinchilla Breeders A. Research Bulletin No. 7, June 1955 (reprinted from Auburn Vet., 1954, **10:** 169).
10. McCoy, E.: Changes in the host flora induced by chemotherapeutic agents. Ann. Rev. Microbiol., 1954, **8:** 257.
11. Jukes, T. H.: Antibiotics in nutrition, in *Antibiotic Monograph Series*, Medical Encyclopedia, Inc., New York, N. Y., 1955.
12. Finland, M.: Emergence of antibiotic-resistant bacteria. New England J. Med., 1955, **253:** 909, 969, 1019.

THE TIRED ARM SYNDROME

A Common Condition Manifest by Nocturnal Pain in the Arm and Numbness of the Hand

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I became interested in this condition during the last World War when I saw a number of patients who had the characteristic symptoms. I had seen only a few such patients previously. At the same time I encountered numerous patients with writer's cramp, restless legs and head-movement vertigo.

The essential *symptoms* are always the same. The patients complain of aching, throbbing pain in the arm, especially the forearm, which resembles a toothache. This develops at night and often awakens the patient from sleep. In some cases the patient thinks that walking the floor gives relief but shortly after returning to bed, is troubled by the pain once more. At the same time, the hand gets numb. In the morning the hand feels stiff and must be massaged before it can be used. During the day the patient notices little or no pain. Numbness does not develop spontaneously, but holding a book or any other act which requires a sustained grip will induce numbness promptly. This numbness disappears as soon as the hand is exercised or massaged. The right arm is involved in right-handed individuals and the left arm in left-handed persons. In some instances both arms are affected but the dominant arm is always more severely involved. Most of my patients are females of middle age though some young women are seen.

The *neurological examination* is always negative. There is never any atrophy or weakness of the muscles. Sensibility is intact and the reflexes are in order. There is no evidence of the hyperabduction syndrome. The pulses are strong at the wrist and no vasomotor abnormalities are found. Roentgenograms of the cervical spine reveal no evidence of herniation of a cervical intervertebral disc or bony proliferation which might cause the symptoms. There is no cervical rib or anomaly of the thoracic outlet.

The cause of this syndrome seems to be excessive muscular exertion, especially unusual exertion. In most instances my patients have been housewives who lost their maids during the war and were forced to wash, sweep, cook and perform other household duties all day long. The wife of one of my friends who had two small children and was a meticulous housekeeper, developed symptoms repeatedly whenever she was deprived of the services of a maid. One unfortunate woman, the wife of a dairy farmer, had continuous symptoms during

a period of 30 years. This patient did all the housework with washing and cooking and in addition helped to wash the milk cans and milk the cows. She was busy from dawn to dusk every day. All night her right arm, which was extremely strong and muscular, ached and her hand was numb. One patient, whose case is given in abstract below, gets symptoms twice a year when she does her semi-annual house cleaning. Painting the house and moving into a new house may be mentioned among the causes. Bowling and riding a horse with a tough mouth may be responsible. Enthusiastic gardening was the cause in one case. Working at a machine in a factory in such a way that one arm is used many times a day may produce this condition.

I believe that this condition occurs in all of us when we put excessive and unusual strain on our muscles. It is possible that some individuals may be more prone to this condition than others, however. In most instances the patient soon recognizes the connection between the symptoms and the fatigue and takes proper measures to get relief. Few seek medical advice.

The *pathogenesis* of this condition is not clear, but it is of interest to mention a somewhat similar syndrome known as shin splints. It is well known that young athletes, especially track men, who start training too vigorously are prone to develop pain, tenderness and swelling of the anterior tibial muscles. Such symptoms pass off in a few days as a rule. It has been suggested that these symptoms may be due to the accumulation of metabolites in the muscles. Possibly the tired arm syndrome may be a result of the same process. Possibly careful measurements of the arm when symptoms are present would reveal swelling of the muscles. If the numbness of the hand represents a real disturbance of sensibility and is not merely a misleading description of stiffness of the muscles, it is hard to explain. One might imagine that swelling of the muscles beneath the antibrachial fascia might cause some compression of the nerves or blood vessels. The fact that there is never any evidence of nerve root damage even after the symptoms have been present for many years, seems to be very strong evidence against the possibility that the symptoms are neurogenic.

The only *treatment* required is rest. In most instances this is satisfactory and the symptoms disappear within two weeks. The advice to rest is not always sufficient, however. Obviously some patients have to work hard to make a living and cannot afford to rest. In others restlessness and nervous tension make it impossible for them to relax and they keep busy even when they have nothing to do. In some instances an obsessive desire for cleanliness drives them on. Sensitive neurotic patients may exaggerate their symptoms and keep them alive with their fears. It is important to explain the symptoms clearly and reassure the patient fully. Sedatives at night to secure a deep restful sleep may be helpful. I have seen patients who have had cervical sympathectomy without relief and others whose symptoms persisted after a scalene muscle was sectioned.

The *prognosis* is good so far as the possibility of persisting disability is concerned. Even in patients who have had symptoms for many years, there is never any loss of function.

Case History: *A left-handed woman of 46 years, has been subject to pain in her left arm and numbness of the left hand twice a year for 8 years. The pain develops every year when she does her semi-annual house cleaning.*

Mrs. L. G., a woman of 46 years, states that twice a year for eight years she has had pain in her left arm and numbness of the left hand. These symptoms always develop when she does her semi-annual house cleaning. She lives in a large apartment with ten rooms and twice a year scrubs the walls, ceilings and floors. She is very particular about having everything spotless. After this period of excessive activity, her arms ache at night so she can't sleep and must walk the floor. During this time her hands get numb during the night and also during the day when she grasps an object firmly for more than a few moments. Such symptoms last for about two weeks after the house cleaning is finished. It should be mentioned that she is left-handed.

The patient's daily routine is a busy one. She does her housework and the cooking and helps her husband in the grocery store in the evenings and on week-ends.

Recently the patient gave up her apartment and moved to a trailer. This promised to make things easier for her. Unfortunately the trailer was heated by an oil burner and everything was covered with oily soot so she had to scrub more than ever. Her symptoms have returned and are worse than ever before. Recently she has had cramps in her legs at night.

The patient is going through the menopause. She is worried about the fact that her husband's business is declining for the chain stores are offering increasing competition. She is worried about her son who is in the Air Force. She has begun to fear she may have some serious trouble in her left arm and may be about to develop paralysis.

I may say very briefly that neurological examination is quite negative. There is no weakness of the left arm or hand and no wasting of the muscles. The reflexes are in order and there is no sensory loss of any kind. Several callosities are found on the palm of the left hand and fingers. The hand is warm and of proper color. The pulses are strong and are not reduced by elevation of the arm or by any movement of the head. Roentgenograms of the cervical spine reveal nothing significant. This patient was seen in consultation with Dr. Robert Mason.

REFERENCES

ADAMS, R. D. AND DENNY-BROWN, D.: *Diseases of Muscle.* Paul B. Hoeber, New York, N. Y. 1953, p. 395.

ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

March 12, 1956

MECHANISMS OF AIRWAY OBSTRUCTION IN PULMONARY EMPHYSEMA

H. B. Martin, E. J. M. Campbell and R. L. Riley

In three normals, three cases of bronchial asthma during attack, and five cases of pulmonary emphysema, pulmonary airway resistance was determined by means of a pneumotachogram for airflow measurement and esophageal balloon for estimating intrapleural pressure. Alveolar pressure was calculated from esophageal pressure by adding the pressure resulting from the elastic retractive force of the lungs as determined at moments of no air flow. During quiet inspiration the mean values of airway resistance (alveolar-mouth pressure difference divided by rate of airflow) for these groups were respectively: 1.7, 16.1, and 6.6 cm. H_2O/liter/sec. at flow rate of 0.5 liter/sec.

When measurements of esophageal pressure and air flow were determined while the subject made a maximal forced expiratory effort, it was found that esophageal pressure continued to rise after flow rate reached a peak. The increase in esophageal pressure was associated with an almost equal increase in alveolar pressure since lung volume, and hence lung elastic retractive force, changed very little in the brief interval before flow rate reached its peak. The continued increase in alveolar pressure without a corresponding increase in air flow indicated a marked increase in resistance after peak flow occurred. The esophageal pressure at which flow rate reached its peak was designated the maximum effective expiratory pressure. Mean values of this for the normals, asthmatics and emphysema patients were respectively: 45, 26, and 9 cm H_2O.

The sharp increase in airway resistance at esophageal pressures in excess of the maximum effective expiratory measure was attributed to forces tending to narrow the airways. Theoretical analysis suggests that the pressure surrounding many of the airways may exceed the pressure in the lumina under these circumstances. Two factors tend to increase the likelihood of such unfavorable transmural pressure relationships. First, any narrowing of the airways due to pathological changes or to bronchospasm increases the pressure gradient along the airway and decreases intraluminal pressure in relation to alveolar pressure. This increases the likelihood that the pressure surrounding the airways will exceed that in the lumina and hence cause further narrowing. Second, any decrease in elastic retractive force of the lung, causing intrapleural pressure (and hence pressure surrounding the airways) to be more positive in relation to intraluminal pressure, makes narrowing more likely.

The resistance during quiet inspiration when the forces tending to narrow the airway were at a minimum was attributed to pathological changes in the airways or to bronchospasm. In comparison with the emphysematous patients, the asthmatics showed higher airway resistance during quiet breathing, higher maximum effective expiratory pressure, and approximately equal maximum velocities of airflow during expiration. These findings suggest that changes in the airways themselves were relatively more important in the asthmatic patients, while loss of elastic retractive force was relatively more important in the emphysematous patients. These differences in pressure-flow relationships may make possible a useful analysis of mechanisms of airway obstruction in patients with obstructive manifestations of unknown cause.

STAPHYLOCOCCAL ENTEROCOLITIS IN CHINCHILLAS

J. Sumner Wood, Ivan L. Bennett, Jr. and John H. Yardley

(Presented by Dr. Wood)

This paper appears in this issue of the Bulletin.

COMPARATIVE IMMUNOCHEMICAL AND HISTOLOGICAL STUDIES ON THE PATHOGENESIS OF ALLERGY OF THE SICKNESS TYPE

Frederick G. Germuth

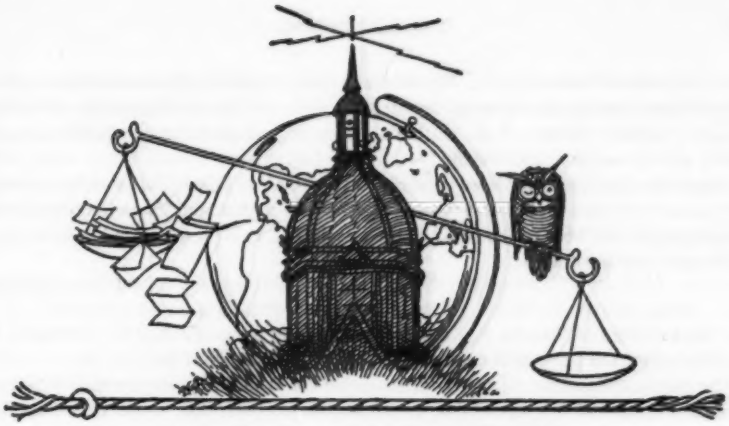
A report was made on the results of histological and immunological studies undertaken to determine:

(a) the relationship between immune response and the evolution of allergic lesions;

(b) the effects of antigen dosage, type of antigen and duration of antigen administration on the development of allergic lesions.

These results bear on the pathogenesis of human allergy.

Finally, preliminary studies undertaken with Dr. Abou Pollack on the production of serum sickness (including periarteritis nodosa) by the passive transfer of antibody were presented. The slow intravenous infusion of antiserum into rabbits treated with antigen has consistently produced periarteritis nodosa. These results show beyond any reasonable doubt that necrotizing arteritis can be produced by antigen-antibody interaction.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Christopher's Textbook of Surgery, 6th edition. Edited by LOYAL DAVIS. 1484 pp., $15.50. W. B. Saunders Co., Philadelphia, Pa.

It is a pleasure to review this new edition of a very standard text and, indeed, it requires a minimum of comment because of its high degree of excellence. It is a long text, being somewhat over 1400 pages. It is thorough in scope and complete in subject coverage without being burdened by unnecessary detail. The contributors, well known in their various fields, have provided uniformly fine chapters and the editor has bound the various sections into a most coherent, readable volume. It will find wide usefulness among students, house officers and as a reference text.

This volume deserves only the highest praise.

JAMES R. CANTRELL.

Heart. A Physiologic and Clinical Study of Cardiovascular Diseases, 2nd edition. By ALDO A. LUISADA. With a Foreword by HERRMAN L. BLUMGART. 680 pp., $15.00. The Williams and Wilkins Co., Baltimore, Md.

The vast accumulation of knowledge in recent years in the field of cardiovascular physiology, both in the normal state and in the presence of disease, makes the recording of a comprehensive survey a task of ever increasing difficulty. The present volume, on the basis of its limited physical dimension alone (680 pages), could not possibly encompass all of the important facets of the field, and in this, as in the earlier edition, there are many aspects of the circulation which are touched upon only lightly. The author has long been interested in mechanical aids in the study of cardiovascular dynamics, and the illustrations reflect this interest. Many controversial features are presented, usually without full documentation of opposing views. The new chapter on cardiovascular syphilis is a case in point. Clinical features are often presented without due indication of their relative importance, and sometimes with greater emphasis on ancillary technical observations than on basic bed-side and historical factors.

Some of the newer aspects of etiology are mentioned in this edition. Similarly, new concepts of therapy are mentioned, including adrenal steroids, the new anti-hypertensive agents,

cardiac resuscitive measures, etc. Discussion of many important new contributions is often quite limited, and in almost every chapter the reviewer has the impression of reading an outline, probably because of the author's efforts to include as many details as possible, even if to only mention them briefly.

This book cannot be considered a definite textbook of cardiology, but should be of especial interest to the person interested in surveying the field with emphasis on the contribution of various graphic methods to the study of the circulation. It is presented in handsome format, and is profusely illustrated.

F. W. DAVIS, JR.

The Biochemistry of Vitamin B_{12}. Biochemical Society Symposia No. 13. Edited by R. T. WILLIAMS. 123 pp., $3.75. Cambridge University Press, New York, N. Y.

The ultimate objectives of many investigations of vitamin B_{12} are the elucidation of the chemical structure of this vitamin, of its mechanism of absorption, and of its metabolic role. These topics are very adequately and critically reviewed by a group of British scientists in the seven chapters of this book.

This book should be very valuable to all those interested in vitamin B_{12} since the therapeutic and nutritional uses of this agent are rapidly being extended through intensive researches now going on.

BACON F. CHOW

Textbook of Endocrinology, 2nd edition. Edited by ROBERT H. WILLIAMS. 776 pp., $13.00. W. B. Saunders Co., Philadelphia, Pa.

Appearing five years after the first edition, this excellent text brings the physician up to date on the many advances that have taken place in this rapidly progressing field of medicine. Much of the book has been rewritten and nearly all of it rearranged; the illustrations are excellent, and the print is set in a different type, making for easier reading.

After a brief discussion of the general principles of endocrinology, the various glands of internal secretion and their disorders are covered in separate chapters. There is perhaps at times too lengthy discussion of physiology and chemistry; e.g., in the chapter on the parathyroids, the complex subject of bone metabolism is treated more exhaustively than seems indicated in a textbook of this type.

There are only a few instances where one would take issue with the text. In discussing the blocking agents used in the diagnosis of pheochromocytoma, Benzodioxane is not recommended because of its disturbing side effects, whereas many workers feel that it is more reliable than the recommended Regitine. Also, in the discussion of the diagnosis of tetany, symptoms of the acute and chronic forms are not clearly separated.

New sections have been added on adrenalectomy for carcinoma and hypertension, on hyperinsulinism and hypoglycemia, and on the use of steroids and ACTH in non-endocrine diseases. The implication that steroids are the treatment of choice in acute rheumatoid arthritis will be questioned by many, however.

Subsequent chapters on the influence of the endocrines on growth and development, obesity, and neuro-endocrinology cover these fields well. In the last section, the author refers too many times to the corresponding chapter in the first edition, as if the reader is expected to have this before him.

The chapter on laboratory procedures has been greatly improved. Each contributor covers his particular field and discusses thoroughly the various tests that are available, both as to technique of preformance and value in diagnosis.

A new concluding chapter nicely summarizes what is and what is not endocrine disease

and succinctly advises the physician regarding the use of hormones. The chemical names of the preparations available are listed, and the physician is urged to use these rather than trade names when prescribing.

The book does not cover gynecomastia and hirsutism as extensively as is desirable but continues to be the best in its field and will prove most valuable to any physician engaged in the practice of medicine or in research in endocrinology.

H. F. KLINEFELTER, JR.

Electrochemistry in Biology and Medicine. Edited by THEODORE SHEDLOVSKY. Sponsored by The Electrochemical Society, Inc., New York, N. Y. 369 pp., $10.50. John Wiley & Sons, New York, N. Y.

This book is the result of a symposium held in New York in 1953. While it really represents three different subjects, a worker concerned with any one of them is likely to gather material of value by reading the book, since all three subjects involve the behavior of ions in solution, which is of interest to biologists.

Each chapter of the book is written by a different author or authors. The first eleven chapters deal with membrane potentials, and discuss both living and non-living systems. The following five chapters are primarily concerned with the physical chemistry of ions in solution. The last three chapters treat electrocardiography, electronencephalography of brain tumors, and the nature of epileptic discharge, respectively.

The book is a sample, though far from complete, of current views held on these subjects in North America. It is recommended as a good place to start in learning about the work that has been done by the various authors.

PHILIP W. DAVIES

Grundfragen der Neurosenlehre. By J. H. SCHULTZ. 215 pp., $5.70. Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

The author treats the subject of "Medical Psychology" (equals U. S. A. "Psychiatry") from an eclectic point of view. Many different schools of thought and concepts are mentioned in a non-critical attitude. For American readers there is some relief in seeing a book that is not strongly slanted to support a special school of psychiatry. The subject of psychiatry is thus treated more in the medical attitude—though not from an exclusively organic point of view—than in the usual psychiatric manner. Although this book is satisfactory for what it does, its deficiencies nevertheless sound to a critical minded reader like the treatises on medicine of 100 years ago, when too little was known of pathological principles for an adequate treatment; thus reminding us of the current primitive state of development of the complex subject of psychiatry.

The publisher, Georg Thieme of Stuttgart, is to be congratulated on the high standard of book making still existing in Western Germany.

W. HORSLEY GANTT

Vitamins in Theory and Practice, 4th edition. By L. J. HARRIS. 366 pp., $6.50. Cambridge University Press, New York, N. Y.

This entertaining little volume presents the story of the vitamins in a simple and readable fashion. Designed for the lay reader, the book provides accurate information concerning the history, chemical structure and biological activity of the known vitamins. Students, nutritionists and others who desire an elementary knowledge of these accessory food factors will find the book profitable and enjoyable. It is in no sense a medical text.

C. LOCKARD CONLEY

Differential Diagnosis of Internal Diseases. Clinical Analysis and Synthesis of Symptoms and Signs on Pathophysiologic Basis, 2nd edition. By JULIUS BAUER. 987 pp., $15.00. Grune & Stratton, New York, N. Y.

This is the second and enlarged edition of an extraordinarily fine book. The author, a clinical professor of medicine, has obviously had an unusually broad experience in practice. The book, therefore, will appeal particularly to the practitioner but it contains much to interest and stimulate both the teacher and clinical investigator. The author discusses in the preface the enormous importance of neurosis in differential diagnosis and the text develops in a most instructive way his views on practical procedure.

The organization of the book is excellent. It is well but not profusely illustrated. The usual charts and tables of more conventional treatises on differential diagnosis are purposely omitted. The index is unusually good; references are very wisely chosen.

This reviewer considers this a most important and valuable source of information on the practical aspects of differential diagnosis.

BENJAMIN M. BAKER

Current Therapy 1955. Edited by HOWARD F. CONN. 692 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

This volume is well arranged and so divided that desired information regarding therapy is readily accessible to the reader. The procedures for treatment are concise and to the point and as stated in the preface, are based on the assumption that the correct diagnosis has been made. This is, of course, a warranted assumption, and should be an added stimulus for the careful assembling of facts and their proper interpretation. Then one may turn to the volume with far greater confidence in one's therapeutic efforts. The list of contributors is an imposing array of talent, each a recognized expert in his particular field, whose advice is worthy to be followed. In the therapy of conditions capable of more than one approach, the opinion of two or more with experience is offered. This not only emphasizes differences of opinion as to the proper therapy, but indicates as well that there are few hard and fast rules that can be laid down.

The section on Infectious Diseases is particularly good. The use of sulphonamides and antibiotics has reached the stage of discriminating selection by the careful physician, when the sensitivity of the offending bacterium to the drug is the determining factor in its use, and the presence of fever is no longer the indication for the use of this group of drugs. It has taken a long time to establish this attitude and whereas the authors have made clear the necessity for the selective approach to the use of antibiotics, more emphasis upon this would be appropriate and desirable. The sections on the Common Cold and those on Viral Diseases in general are to be commended in particular as they point out the ineffectiveness of antibiotics in viral diseases, and deplore their careless use. Would that more emphasis had been put upon the indiscriminate use of antibiotics, and the actual danger which such use may entail.

The division of the volume into sections is, of course, necessary to make it readily usable, and such division is in the main good, even though it may create a sharper delineation of disease than is always desirable. It is a bit disconcerting to find the treatment of glomerulonephritis, renal failure and uremia in the section with urethritis and Peyronie's Disease. The section on Diseases of the Nervous System is worthy of comment in that the limited therapeutic possibilities in so many of its affections are forthrightly acknowledged and a conservative approach is employed where such limitations exist. Such an attitude inspires confidence in the volume as a whole. In other sections some therapeutic procedures advised are a bit radical but in most their real worth is established. It is to be hoped, however, that

such a cataloguing of disease will not tend to cause the doctor to forget to treat his patient as an individual as well as his disease.

Current Therapy is to be commended to every practicioner of medicine and its use urged. Desired information as to treatment which is proved by experience is available here, and if it does nothing more than draw the doctor away from advertising brochure therapy it is eminently worthwhile, but sound advice is obtainable for the seeking.

CHARLES W. WAINWRIGHT

Medical Treatment of Mental Disease. By DANIEL J. MCCARTHY AND KENNETH M. CORRIN. With Sections by Eight Contributors. 653 pp., $12.00. J. B. Lippincott Co., Philadelphia, Pa.

This six hundred and fifty-three page volume is dedicated to Dr. Silas Weir Mitchell. The authors organize their book into first, general considerations, then a classification of mental disorders, including a large emphasis on the "organic" mental illnesses. Other sections are on basic treatment methods and medico-legal aspects of psychiatry.

The point of view of Doctors McCarthy and Corrin is stated repeatedly in a number of ways, all meaning approximately the same thing to this reviewer. A sample of this point of view is as follows on page 4 in the introductory section of the book called "The Physical Basis of Psychiatry"; "Mental disease is a perversion of function of the brain, a deviation from the normal in certain underlying processes. It is the authors' conclusion that these disturbances are uniformly organic in origin and produced by changes in the nerve cell, although specific etiology in many instances still remains unknown." On page ix of the preface the authors state, "We recognize that emotional factors are important, constituting a part of the illness, but we believe that they represent effects of disease, not causes."

This reviewer finds the book alien to his training as an internist and psychiatrist, and his experience in treating and diagnosing patients with emotional problems of serious degree. The authors show a curious ambivalent attitude toward psychodynamic psychiatry. On the one hand they quote leading psychoanalytic authors, and on the other they completely reject well known and daily used principles of dynamic psychiatry.

Recognition of mental mechanisms (for example, repression and denial) which are the everyday concerns in the work of the psychiatrist in formulating problems and dealing in a practical way with patients, is almost completely absent in this book. The problem of anxiety, which is foremost in dealing with the emotional aspects of mental life, in health and in disease, is nowhere mentioned or formulated in this book. Lip service is paid to many of the ideas current in the last thirty years in dynamic psychiatry, but the reader gains the impression that the authors are not in accord with these views and feel that to be "scientific" they must resort to an organic etiology, a tangible, mathematical, measurable entity in order to understand and to present their ideas. No serious clinically experienced student of human behavior would deny the organic basis for all behavior and function.

The descriptive aspects of some types of mental illness, the shock therapies, and legal aspects are informative.

This volume reminds one of the scene in "A Christmas Carol" by Charles Dickens, that intuitive humanitarian, who presents the picture of Scrooge on first seeing Marley's ghost. Marley's ghost says "What evidence would you have of my reality beyond that of your senses?" "I don't know," said Scrooge. "Why do you doubt your senses?" "Because," said Scrooge, "A little thing affects them. A slight disorder of the stomach makes them cheats. You may be an undigested bit of beef, a blot of mustard, a crumb of cheese, a fragment of an underdone potato. There's more of gravy than of grave about you, whatever you are!" Dickens here recognizes that Scrooge is dealing with anxiety. The authors of the book under

review do not see human personality working in such a functional way. Apparently the problem of meaning is not considered by Doctors McCarthy and Corrin. Meaningful emotions must be considered whether the treatment of mental disease be pharmacological, surgical or psychological.

WILLIAM T. DIXON

Urology. Edited by MEREDITH CAMPBELL; 3 volumes, 2356 pages, $60.00. W. B. Saunders Co., Philadelphia, Pa.

The gigantic work published under the editorship of Dr. Campbell is the combined effort of 52 collaborators. The entire field of urology is handled in encyclopedic fashion by recognized authorities in the various topics.

Being published some 20 years since the last similar effort, this work fulfills a real need. The field of urology has greatly expanded during this interval primarily by the assimilation of basic science discoveries and secondarily by liberalization of surgical indications permitted by the concurrent advancement in surgical techniques, management of blood loss, anaesthesia, and the treatment of infections. Thus, there was need to synthesize in one publication the present concepts of urologic diseases and their current management. This synthesis of modern urology, the avowed objective of the editor, has been accomplished in an admirable fashion.

Great variation exists in the quality of the individual contributions. Most are excellent; several are outstanding monographs of the subject treated and reflect not only the broad knowledge of their authors but also show painstaking care in manuscript preparation and bibliography selection. A few chapters fall below expected standards. Unfortunately the management of hypospadias is one of them. The tone of most of the chapters is somewhat didactic but there is sufficient overlap between them so that seasoned opinion is generally registered.

If there is any serious defect in these volumes, it is, in this reviewer's opinion, the relative lack of cross references between discussions of the basic phenomena of a condition and the unabridged discussion of its clinical management. This detracts from facile utilization of the volumes as a reference work, but is partly compensated for by the excellent chapter bibliographies.

The work seems destined for a place beside its classic predecessors such as those of Hinman, Young, and Cabot. It will be useful to practicing urologists, general surgeons doing some urology, and urologic residents. It especially deserves a place in the libraries of all institutions training surgical and urologic residents.

WILLIAM J. HOPKINS

BOOKS RECEIVED FOR REVIEW

Biochemical Mechanisms in Inflammation, 2nd edition. (American Lecture Series). By VALY MENKIN. 438 pp., $9.50. Charles C Thomas, Springfield, Illinois.

Clinical Electrocardiography. I. Arrhythmias. With an Atlas of Electrocardiograms. By LOUIS N. KATZ AND ALFRED PICK. 737 pp., $17.50. Lea & Febiger, Philadelphia, Pa.

Clinical Laboratory Diagnosis, 5th edition. By SAMUEL A. LEVINSON AND ROBERT P. MACFATE. 1246 pp., $12.50. Lea & Febiger, Philadelphia, Pa.

Diseases of the Chest. By H. CORWIN HINSHAW AND L. HENRY GARLAND, 727 pp., $15.00. W. B. Saunders Co., Philadelphia, Pa.

A Modern Pilgrim's Progress for Diabetics. By GARFIELD G. DUNCAN. 222 pp., $2.50. W. B. Saunders Co., Philadelphia, Pa.

The Neuroses in Clinical Practice. By HENRY P. LAUGHLIN. 802 pp., $12.50. W. B. Saunders Co., Philadelphia, Pa.

Obstetric Practice. By HAROLD SPEERT AND ALAN F. GUTTMACHER. 478 pp., $7.00. Landsberger Medical Books, Inc., distributed solely by The Blakiston Division of The McGraw-Hill Book Co., New York, N. Y.

An Outline of the Cytology and Pathology of the Reticular Tissue. With a Chapter on the Lipidoses by J. B. CAVANAGH. By A. H. E. MARSHALL. 274 pp., 42/-net. Oliver & Boyd Ltd., Edinburgh, Scotland.

Shock and Circulatory Homeostasis. Transactions of the Fourth Conference December 6, 7 and 8, 1954. Edited by HAROLD D. GREEN, 291 pp., $5.00. The Josiah Macy, Jr. Foundation, New York, N. Y.

Surgical Diagnosis. By PHILIP THOREK. 320 pp., $12.00. J. B. Lippincott Co., Philadelphia, Pa.

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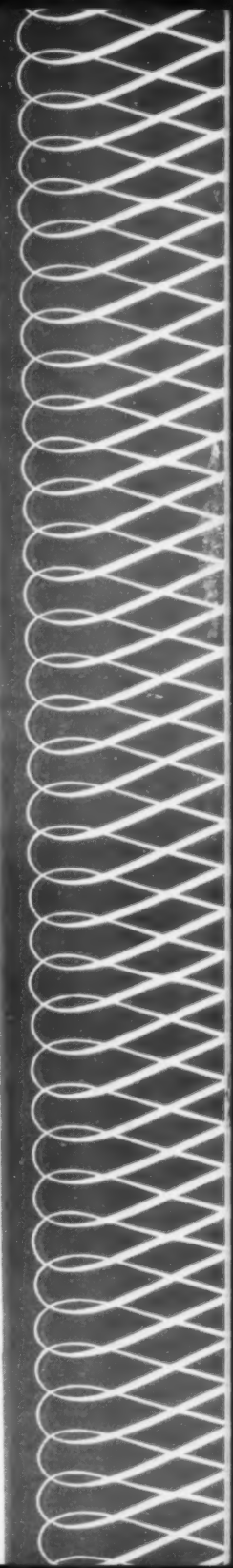

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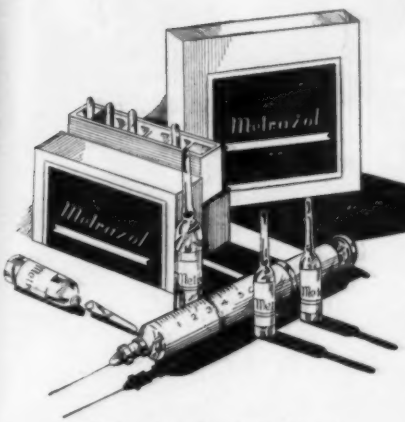

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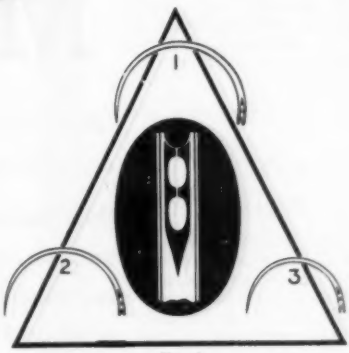

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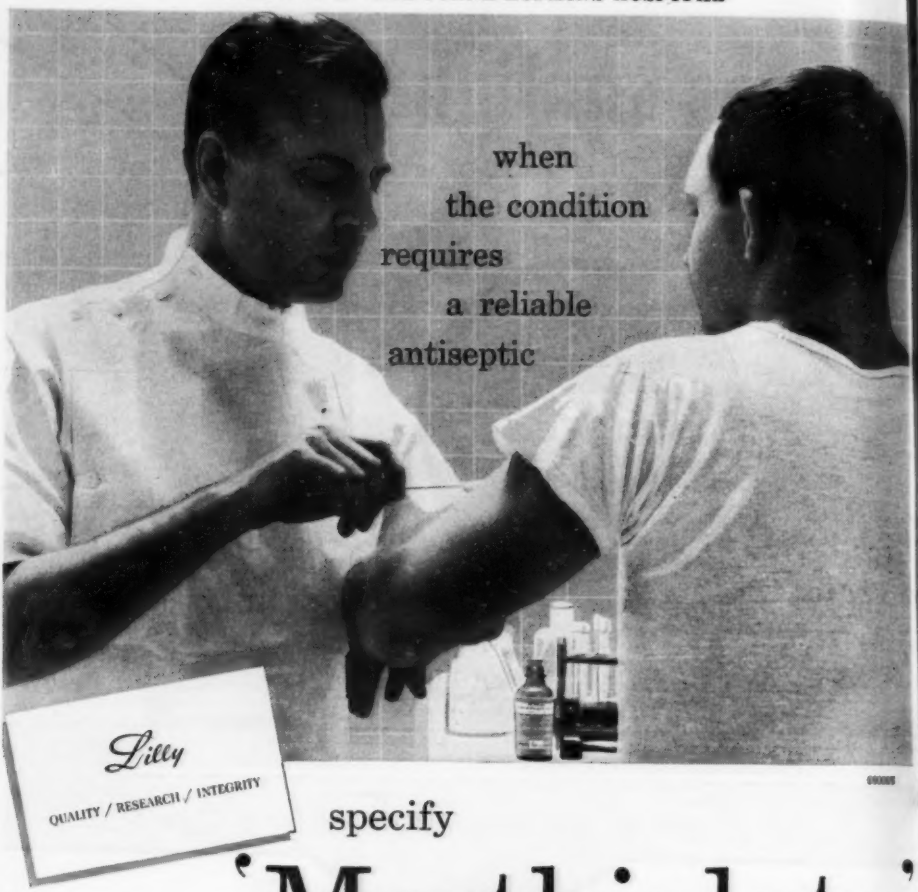

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